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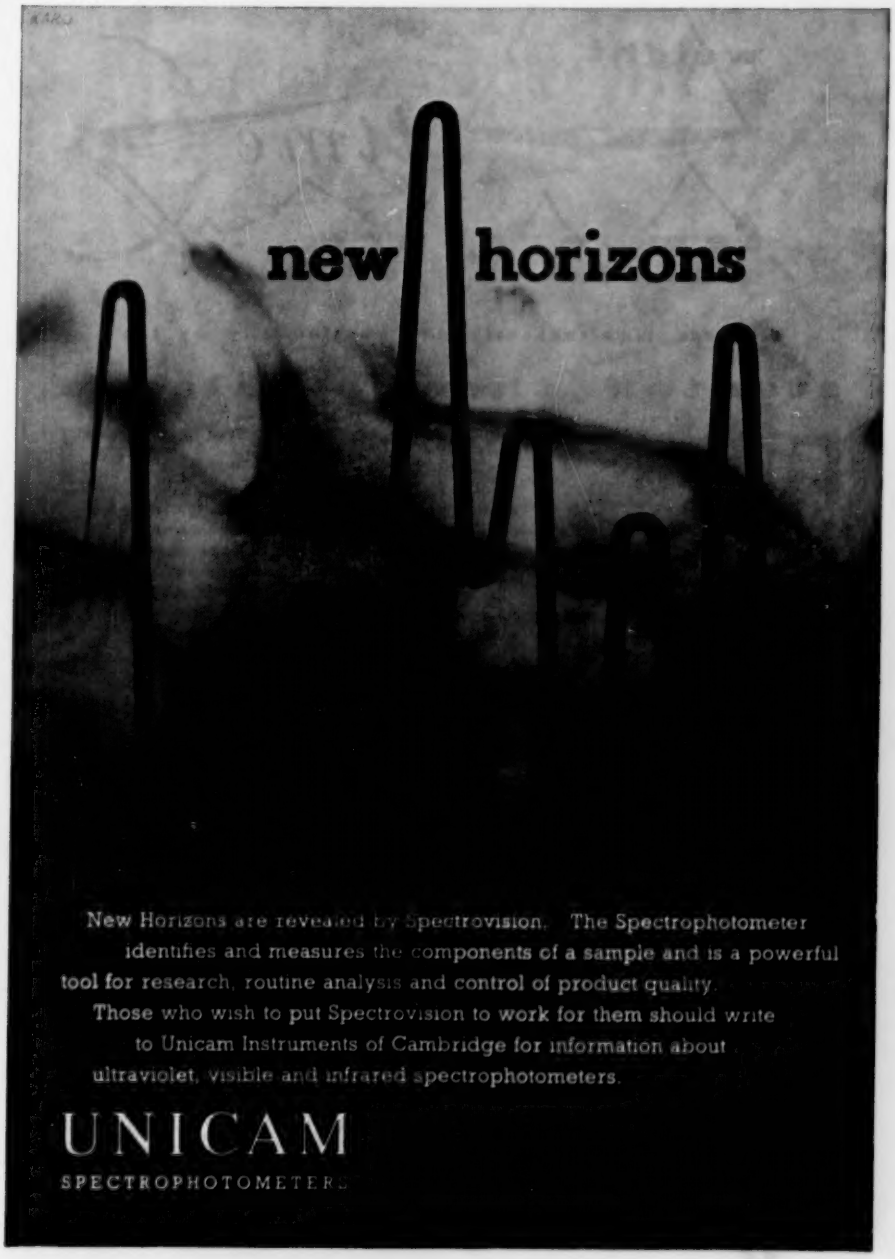
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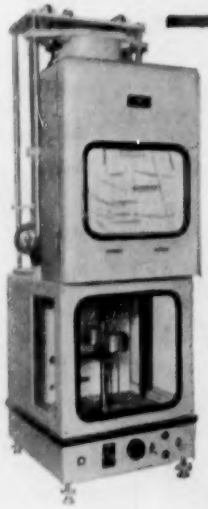

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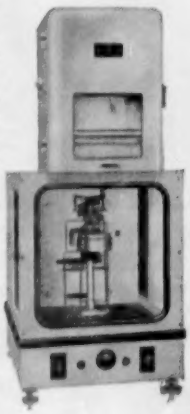

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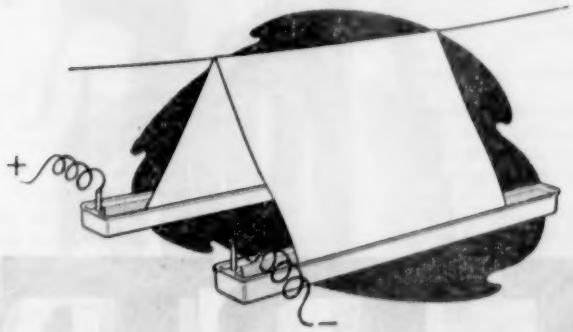

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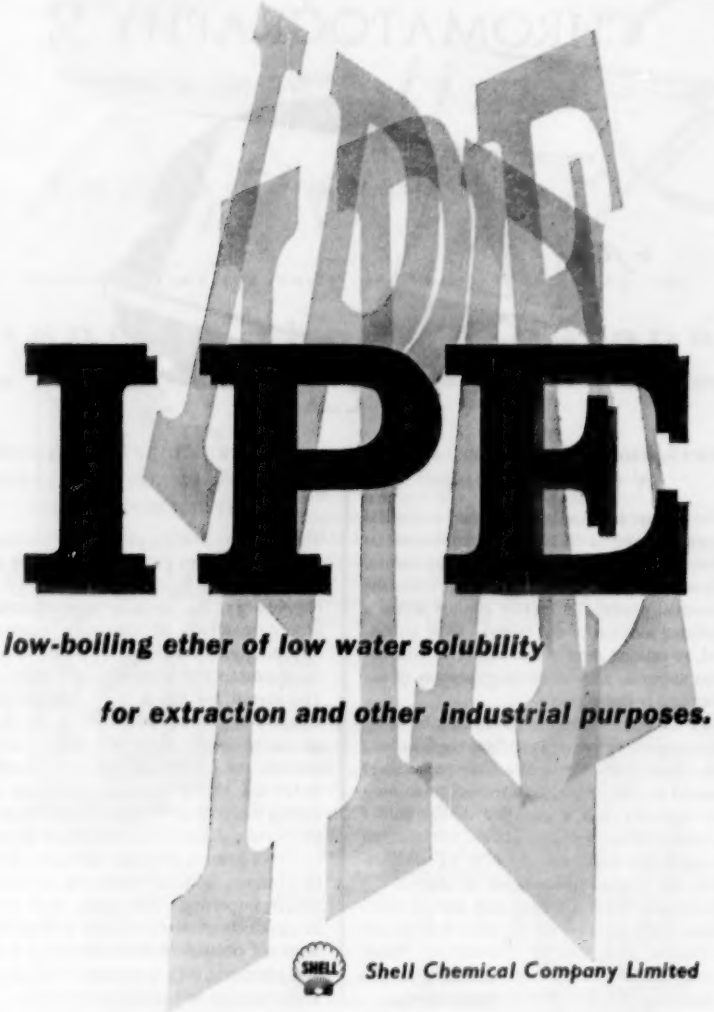

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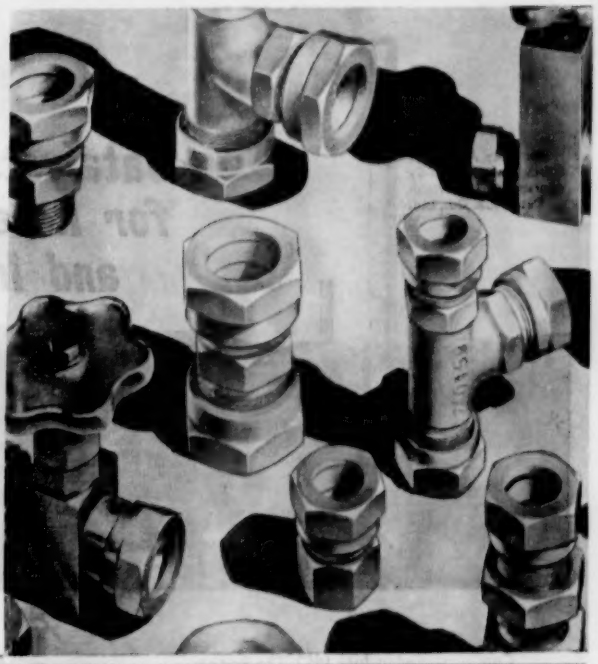

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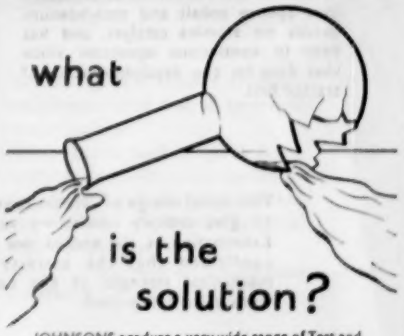

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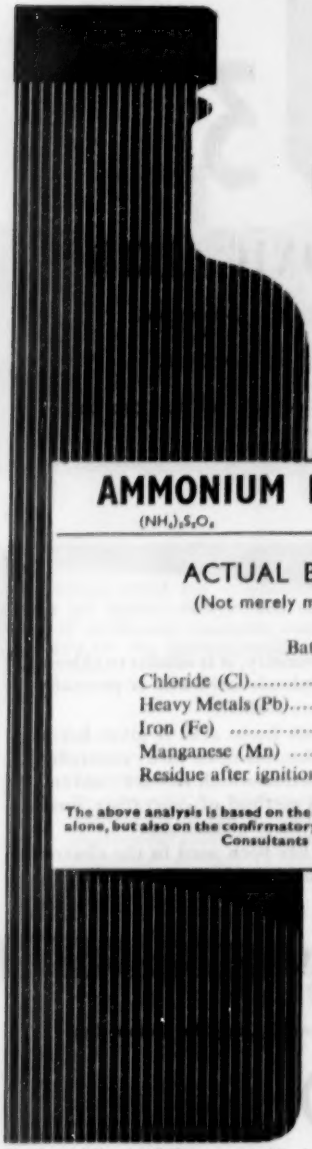

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Nyholm, R. S. See also Ingold, C. K., **1691**.
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Owen, B. D. R. See Davies, C. W., **1676**, **1681**.
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Shaw, G. See Ralph, R. K., **1877**.
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Singer, N. See French, C. M., **1424**.
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Soliman, G. See Kenyon, J., **1774**.
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Stirling, C. J. M. See Hey, D. H., **1475**.
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Strachan, W. S. See Brownlie, G., **1377**.
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Summers, G. H. R. See Shoppee, C. W., **1649**, **1893**.
Swan, G. A., and Wright, D., **1549**.
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Thomas, A. F. See Bentley, K. W., **1863**.
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Tittensor, E. See also Fraser, J., **1781**.
Tobe, M. L. See Ingold, C. K., **1691**, and Nyholm, R. S., **1707**.
Todd, Sir A. R. See Chase, B. H., **1371**, and Michelson, A. M., **1546**.
Topham, A. See Kiang, A. K., **1319**.
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Warwick, G. P. See Ross, W. C. J., **1364**, **1719**, **1724**.
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Webb, R. F. See Chase, B. H., **1371**.
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Wibberley, D. G. See Tittensor, E., **1778**.
Williams, G., and Clark, D. J., **1304**.
Williams, G. H. See Hey, D. H., **1463**, **1475**.
Williams, R. J. W. See Shoppee, C. W., **1893**.
Wood, G. A. See Arden, T. V., **1596**.
Woodford, F. P. See Milburn, A. H., **1740**.
Wright, D. See Swan, G. A., **1549**.

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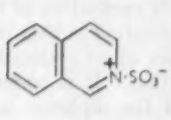
259. *The Ring Fission of* iso*Quinoline–Sulphur Trioxide.*

By K. T. Potts.

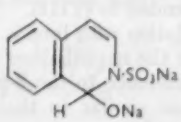
The disodium salt of 1 : 2-dihydro-1-hydroxy*iso*quinoline-2-sulphonic acid (II) is proposed as the constitution of the product obtained by the action of cold aqueous sodium hydroxide on *iso*quinoline–sulphur trioxide.[1]

Baumgarten and Olshausen [1] first investigated the action of cold, aqueous sodium hydroxide on *iso*quinoline–sulphur trioxide (I) and concluded that ring fission occurred, giving a salt (III). The colourless acid, obtained from the salt on treatment with dilute acids, was designated as (IV). This is analogous to the intermediates assumed to be formed in the hydrolysis of pyridine–sulphur trioxide.[2]

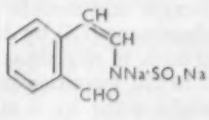
On re-investigation of this reaction it became apparent from spectral studies that the structure of the product obtained was more correctly represented as (II), the disodium salt of 1 : 2-dihydro-1-hydroxy*iso*quinoline-2-sulphonic acid.



(I)



(II)



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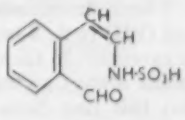


(IV)

The empirical formula was confirmed as $C_9H_7O_4NSNa_2,2H_2O$ and its properties agreed with those previously reported. The infrared spectrum (in Nujol) showed absorption bands at 2·90 (s) * (an associated OH from the water of crystallisation present), 6·14 (m) (aromatic nucleus), and 8·10 and 8·45 μ (s) (sodium sulphonate group). The most significant feature was the absence of carbonyl absorption which should be present for a compound (III). [In the spectrum (Nujol) of the monosodium salt of glutacondialdehyde [3] a characteristic carbonyl absorption band occurs at 6·25 μ (vs), the absorption at slightly longer wavelength (usual absorption, *ca.* 5·9 μ) being due to the extensive conjugation and high symmetry of the molecule.]

The acid liberated by treatment of this salt with dilute acid should likewise have infrared carbonyl absorption if it were correctly represented by (IV). Its spectrum was found to be identical with that of the original *iso*quinoline–sulphur trioxide (I); it had the general broad absorption of salts, a band at 6·25 μ (m) which experience in this laboratory has indicated is generally associated with the carbon–nitrogen double bond present in *iso*quinolinium salts (6·2—6·3 μ), and bands at 9·45 and 9·55 μ (s) (sulphonic anhydride). [In a recent paper, Witkop [4] regards salt formation in pyridines as causing an absorption at 6·07—6·13 μ.] The analytical results and properties of this compound agree with this interpretation and the m. p. was not depressed on admixture with freshly prepared *iso*quinoline–sulphur trioxide.

The ultraviolet spectra of *iso*quinoline–sulphur trioxide (I) (max. at 2650, 2750, and 3320 Å) and the sodium salt (II) (max. at 2750 and 3350 Å) are analogous to those of cotarnine hydrochloride [5,6] (max. at 2500 and 3278 Å, ammonium form) and aqueous solutions of the hydrochloride in the presence of an excess of 2N-sodium hydroxide (ill-defined max. at 2875 Å, carbinol form) and berberine.[6]

A solution of the salt (II) in 50% ethanol had pH 11·8 and on titration with 0·1N-hydrochloric acid the neutralisation curve indicated the presence of a strong base. An

* Usual convention.

[1] Baumgarten and Olshausen, *Ber.*, 1931, **64**, 925.
[2] Baumgarten, *Ber.*, 1926, **59**, 1166.
[3] *Idem*, *Ber.*, 1924, **57**, 1622.
[4] Witkop, *Experientia*, 1954, 420.
[5] Dobbie, Lauder, and Tinkler, *J.*, 1903, **83**, 598.
[6] Skinner, *J.*, 1950, 823.

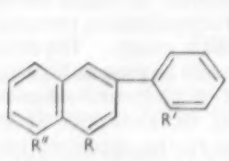
inflexion occurred at pH 4·3 and is due to a process involving addition of a proton to the sulphonate ion and then immediate elimination of water from the resulting sulphonic acid. However, the presence of a strong base in solution can be explained by both formulæ; for a structure (IV) it would be expected that the imino-hydrogen atom would be weakly acidic and the sodium salt (III) would give an equivalent of hydroxyl ions in solution. A similar argument may be used for a structure (II).

Attempts to show that the salt (II) undergoes the normal reactions of *pseudo*-bases, *e.g.*, ether formation and the reaction with nitromethane, were unsuccessful owing to the instability of the molecule.

This type of carbinolamine formation is well established in the *iso*quinoline series, *e.g.*, the carbinolamines derived from 2-methyl*iso*quinolinium salts [7] and various *iso*quinoline alkaloids.

As shown recently,[8] the further action of hot, aqueous sodium hydroxide on the compound (I) affords 4 : 2′-diformyl-2-phenylnaphthalene (V) and not the dialdehyde (VI) as stated by Baumgarten and Olshausen. Hence the naphthalenedicarboxylic acid prepared by the above authors has structure (VII) and accordingly the structure of their 1 : 2-benzofluorenonecarboxylic acid must be amended to (VIII). Their cyclisation of the acid (VII) to 2 : 3-benzofluorenone (IX) by distillation with lime is interesting in that it is an exception to the usual mode of ring closure in the naphthalene series where cyclisation almost always occurs on to the 1-position in preference to the 3-position. It is possible that this ring closure might occur by a method similar to that of the diphenic acid cyclisation,[9] but a more attractive explanation is as follows.

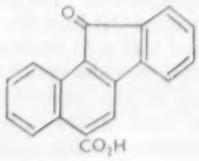
Under the influence of heat there is a tendency for carbon dioxide to be eliminated from the calcium salt of (VII). This leaves a negative charge at position 4, and, after prototropic



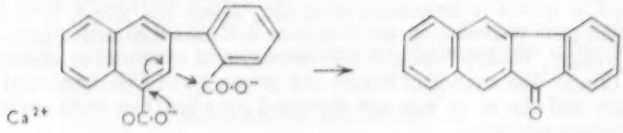
(V): R=R′=CHO, R″=H

(VI): R′=R″=CHO, R=H

(VII): R=R′=CO_2H, R″=H



(VIII)



(X) (IX)

rearrangement of the hydrogen atom from the 3- to the 4-position of the naphthalene nucleus, a negative charge on the 3-position. The final step probably involves a nucleophilic attack of the 3-position on the carbon atom of the other carboxylate ion. This scheme is represented in (X). No close formal analogy to such a 1 : 2-prototropic rearrangement can be recalled but it would not be surprising in view of the reaction conditions employed.

Several improvements in the original methods employed by Baumgarten are described in the Experimental section.

[7] Robinson and Robinson, *J.*, 1914, **105**, 1456.
[8] Potts and Robinson, *J.*, 1955, 2466.
[9] Fittig and Ostermayer, *Annalen*, 1873, **166**, 372.

Experimental

Light absorptions refer to MeOH solutions.

Treatment of iso*Quinoline–Sulphur Trioxide with Alkali.*—*iso*Quinoline–sulphur trioxide [8] (2·1 g.) was triturated with ice-cold sodium hydroxide solution (2·4 g. in 7 c.c. of water) with cooling in an ice-salt bath. An immediate yellow colour was produced and the material soon set to a paste. Washing with cold alcohol removed the yellow impurity and the white, crystalline *disodium salt* of 1 : 2-dihydro-1-hydroxy*iso*quinoline-2-sulphonic acid (3·6 g.) was collected and dried (Found : C, 35·4; H, 4·4; Na, 15·0, 15·2. $C_9H_7O_4NSNa_2.2H_2O$ requires C, 35·2; H, 3·6; Na, 15·0%). Light absorption : $\lambda_{max.}$ 2350, 2750, 3350 Å (log ε 4·40, 3·58, 3·38), $\lambda_{min.}$ 2500, 3000 Å (log ε 3·22, 3·14).

Treatment of the Disodium Salt with Acid.—A solution of the disodium salt (3·6 g.) in water (50 c.c.) was made just acid to litmus with dilute hydrochloric acid; an immediate white precipitate was formed. When washed with ice-water, and dried, this had m. p. 253—256°, not depressed on admixture with freshly prepared *iso*quinoline–sulphur trioxide (Found : C, 51·8, 51·3; H, 3·7, 3·3; N, 7·3, 6·8. Calc. for $C_9H_7O_3NS$: C, 51·6; H, 3·4; N, 6·8%). Light absorption : $\lambda_{max.}$ 2300, 2650, 2750, 3320 Å (log ε 4·38, 3·44, 3·44, 3·72), $\lambda_{min.}$ 2500, 2700, 2950 Å (log ε 3·23, 3·43, 3·05).

2-*Phenylnaphthalene*-2′ : 4-*dicarboxylic Acid.*—2-Phenylnaphthalene-2′ : 4-dialdehyde [9] (2·0 g.) and potassium permanganate (2·0 g.) in acetone (50 c.c.) were refluxed for 90 min. After 12 hr. at room temperature the manganese dioxide was filtered off and suspended in water (30 c.c.), and sulphur dioxide passed into the mixture. The manganese dioxide was replaced by pale cream-coloured needles (2·0 g., 89%), m. p. 258—268° after shrinking at *ca.* 240°. 3-*o*-*Carboxyphenyl*-1-*naphthoic acid*, crystallized from 50% methanol, had m. p. 261—262° after shrinking (Baumgarten and Olshausen reported m. p. 267—268° (Found : C, 74·2; H, 4·3. $C_{18}H_{12}O_4$ requires C, 74·0; H, 4·1%). Light absorption : $\lambda_{max.}$ 2400, 2950 Å (log ε 4·38, 3·77), $\lambda_{min.}$ 2800 Å (log ε 3·73). The acid gave a yellow colour, changing to a dirty brown on warming, with concentrated sulphuric acid; it was only slightly soluble in concentrated nitric acid, and, on warming, gave a yellow solution with evolution of brown fumes.

2-*Phenylnaphthalene.*—The above dicarboxylic acid (200 mg.), copper bronze (200 mg.), and quinoline (5 c.c.) were heated under reflux for 30 min. After cooling, the mixture was diluted with ether and extracted with dilute hydrochloric acid (3 × 10 c.c.). The ether solution was washed with water and dried (Na_2SO_4). The small amount of oil left on evaporation soon crystallized. It separated from aqueous methanol (charcoal) as white plates, m. p. 100—101° (Breuer and Zincke [10] record m. p. 101·5°).

1 : 2-*Benzofluorenone.*—1 : 2-Benzofluorenone-3-carboxylic acid (200 mg.) was heated with copper bronze (300 mg.) in quinoline (5 c.c.) for 30 min. Working up as in the preceding experiment, but with alkali washing, gave 1 : 2-benzofluorenone, orange-red needles (from methanol; charcoal), m. p. 132° (Bamberger and Burgdorf [11] report m. p. 132·5°) (Found : C, 88·8; H, 4·8. Calc. for $C_{17}H_{10}O$: C, 88·6; H, 4·4%). Light absorption : $\lambda_{max.}$ 2700, 3725 Å (log ε 4·77, 3·54), $\lambda_{min.}$ 3300 Å (log ε 3·13).

I thank Professor Sir Robert Robinson, O.M., F.R.S., for encouragement and advice.

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[*Received, August 31st*, 1955.]

[10] Breuer and Zincke, *Ber.*, 1878, **11**, 1404.
[11] Bamberger and Burgdorf, *Ber.*, 1890, **23**, 2439.

260. *Studies in Hydrogen-bond Formation. Part V.* Complex-forming Properties of Esters, and their Relation to the Adsorption Properties of Cellulose Acetate and Other Polymers.*

By F. M. Arshid, C. H. Giles, and S. K. Jain.

The complex-forming reactions of a variety of compounds containing the grouping $CO{\cdot}CH_3$, in aqueous and non-aqueous solutions, have been investigated by measurements of dielectric constant, refractive index, and infrared absorption. Esters appear to act as monofunctional proton-donors. Diacetates are normally bifunctional proton-donors, but when the two acetate groups are vicinal they interact, probably by chelation through a Ch $\cdots$ hydrogen bond, and the compound is monofunctional. *N*-Acetylglucosamine appears to form bonds through the amino-group; its hydroxy-groups are also active in non-aqueous solvents but not in water.

The results are considered to be significant in the interpretation of the adsorption behaviour of cellulose acetate, chitin, and Terylene.

This investigation is principally a study of the hydrogen-bonding reactivity of esters, made with a view to determine the importance of this bonding in adsorption of solutes by chitin, cellulose acetate, and other polymeric esters; the technique has already been described.[1,2] Various acetates and *N*-acetylglucosamine have been used as models of cellulose acetate and chitin, respectively, and dimethyl terephthalate and ethylene glycol dibenzoate as models of polyethylene glycol terephthalate (Terylene). The results are shown in Table 1 and Figs. 1 and 2, and are discussed below.

Experimental

The general method has already been described;[1,2] in this work the Bellingham and Stanley (new model) Pulfrich refractometer was mainly employed, though some tests were made with the two instruments used for Part II.[2] The solvents and reagents were commercial or laboratory-prepared materials purified by standard methods.

It has been found that some systems give better results if the solutions are kept overnight before measurement, no doubt because the solutes have a low reaction or solution rate.

Catechol diacetate, prepared by mixing catechol and acetyl chloride in the cold, followed by addition of water, and recrystallisation from ethanol, formed needles, m. p. 63·5°.

3-Methoxybenzanthrone was a sample of Duranol Brilliant Yellow 6G (I.C.I.) recrystallised from benzene. (This was used as a typical cellulose acetate dye.)

Pentane-1 : 5-diol diacetate. Pentamethylene glycol was refluxed with excess of acetic anhydride and dry pyridine for 2 hr. The mixture was then washed successively with water, dilute acetic acid, and sodium carbonate solution. The oily layer was extracted with ether and redistilled, and the distillate kept over sodium to ensure removal of all traces of unesterified diol; the ester had b. p. 240°, f. p. 6°.

The glycerol triacetate used in the Rhodamine B test was also allowed to remain over sodium to remove unchanged alcohol.

Quinol diacetate was prepared by mixing quinol, acetic anhydride, and a few drops of sulphuric acid, in the cold. The product which separated recrystallised from ethanol as plates, m. p. 121°.

A Grubb-Parsons double-beam infrared spectrophotometer (sodium chloride prism) was used.

Infrared spectra. Catechol diacetate and quinol diacetate were examined as 1·5% CCl_4 solutions (0·8 mm. cells) and ethylene glycol diacetate and pentane-1 : 5-diol diacetate both as 1·5% CCl_4 solutions (0·8 mm. cells) and as pure liquids (0·025 mm.); Catechol diacetate and quinol diacetate both show a carbonyl peak at 1776 cm.$^{-1}$, while the former, but not the latter, has an additional peak at 1727 cm.$^{-1}$. There was no apparent difference between their CH_3

* Parts III and IV, *J.*, 1956, 72, 559. In Part IV, the first line on p. 569, free acid *should read* on free acid.

[1] Part I, Giles, Rose, and Vallance, *J.*, 1952, 3799.
[2] Part II, Arshid, Giles, McLure, Ogilvie, and Rose, *J.*, 1955, 67.

symmetrical deformation bands at 1381 cm.$^{-1}$; a CH_3 symmetrical deformation band appears at 1439 cm.$^{-1}$ in quinol diacetate, while in catechol diacetate two peaks appear at 1443 cm.$^{-1}$ and 1468 cm.$^{-1}$. The C–O stretching peak at 1190 cm.$^{-1}$ (very broad) in quinol diacetate is shifted, and new peaks at 1205 and 1175 cm.$^{-1}$ appear instead.

No significant differences are apparent between the C=O bonds of ethylene glycol diacetate and pentane-1 : 5-diol diacetate; the centre of the broad C–O acetate band at 1070 cm.$^{-1}$ in the former is at 1050 cm.$^{-1}$ in the latter, and that of the C–O stretching band at 1247 cm.$^{-1}$ in the former shifts to 1258 cm.$^{-1}$ in the latter. In the CCl_4 solutions the CH_3 symmetrical deformation band at 1381 cm.$^{-1}$ occurs in both spectra, but a band at 1403 cm.$^{-1}$, probably also a CH_3 symmetrical deformation (cf. ref. 18) which occurs in the spectrum of pentane-1 : 5-diol diacetate, is not present in that of ethylene glycol diacetate. This change is not apparent in the spectra of the pure liquids because the absorption is too strong.

Discussion

N-*Acetylglucosamine* (cf. Fig. 1).—This appears to be a monofunctional proton donor in water, probably through the acetyl group at the nitrogen atom or the carbon atom in the

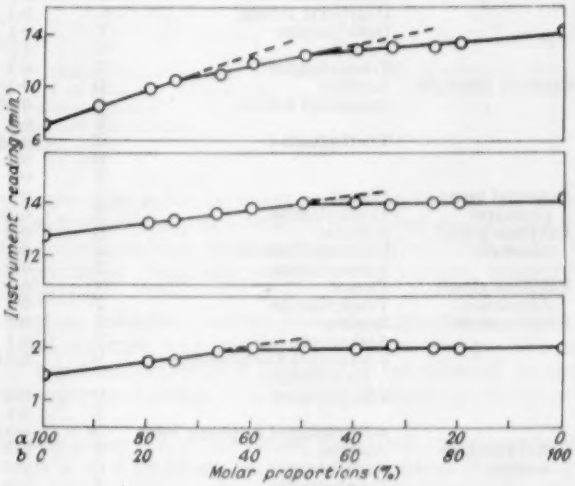


Fig. 1. *Relation between refractive index (as instrument reading) and component ratio in solutions of binary systems.*

Top : *a*, Triethylamine; *b*, glycerol triacetate. Solvent, water.
Middle : *a*, Di*iso*butyl ketone; *b*, ethylene glycol diacetate. Solvent, dioxan.
Bottom : *a*, Di*iso*butyl ketone; *b*, pentane-1 : 5-diol diacetate. Solvent, toluene.

methyl residue, the hydroxy-groups being solvated and the molecule acting in the ring-form; * in ethylene glycol solutions 1 : 1 and 1 : 4 complexes are detected between this compound and alcohols or phenols, and in these cases three of the hydroxyl groups must also be reactive; the fourth is probably chelated, thus as in (*A*) (p. 1276). This type of chelate bond has been suggested by Darmon and Rudall [3] as existing (together with free >NH groups) in chitin, on the evidence of studies with polarised infrared and *X*-radiation.

Reactivity of Esters.—It is clear from the results shown in Table 1 that all the esters examined can interact with electron donors, *e.g.*, azobenzene, pyridine, or triethylamine, both in non-polar solvents and in water. It seems likely that this takes place through a –C–H · · · O or –C–H · · · N bridge facilitated by the enhanced lability of the carbon–hydrogen bond adjacent to a carbonyl group. The active C–H bond in some cases appears to be that attached α to the O–C=O group (*e.g.*, in ethylene glycol dibenzoate †) and in others α to the –C=O group (*e.g.*, in the acetates). For further examples, compare, respectively,

* Compare the inactivity of the hydroxy-groups in the ring forms of the carbohydrates in water (Part IV, *loc. cit.*).

† The existence of three examples of this type of complex is suggested also by molecular-weight determinations (Part II,[2] Figs. 8, 9, 10).

[3] Darmon and Rudall, *Discuss. Faraday Soc.*, 1950, **9**, 251.

TABLE 1. *Results of complex-detection tests.*

Solution: Solutes *a*	Solution: Solutes *b*	Solvent *	Total molar concn.	Method(s) † and temp.	Mol. ratio ‡ of complex, *a* : *b*
Acetyl chloride	Acetone	C	0·2	*n* 19°	1 : 1
	Azobenzene	D	0·1	*n* 22	2 : 1
Benzyl acetate	Acetone	T	0·1	*n* 22·5	§
	Dioxan	T	0·1	*n* 22·5	§
	Pyridine	T	0·1	*n* 24	§
N-Acetyl-D-glucosamine	Methanol	W	0·25	*n* 19	1 : 1
		EG	0·1	*n* 18	1 : 1; (1 : 4)
	β-Naphthol	EG	0·05	*n* 18	(1 : 1); 1 : 4
	Phenol	EG	0·05	*n* 16, 18	1 : 1; 1 : 4
		W	0·25	*n* 18	1 : 1
	Triethylamine	W	0·25	*n* 20	1 : 1
	Quinol	W	0·25	*n* 20	2 : 1
2-Acetylpyridine	Acetone	T	0·1	*n* 21	(§)
	Triethylamine	T	0·1	*n* 21	1 : 1
3-Acetylpyridine	Acetone	T	0·1	*n* 21·5	§
	Pentyl alcohol	T	0·1	*n* 22	1 : 1
	Azobenzene	T	0·1	*n* 19·5	(§)
	Di*iso*butyl ketone	C	0·1	*n* 21	§
	Diethylamine	T	0·1	*n* 21	1 : 1
	Pyridine	T	0·1	*n* 19·5	(§)
	Triethylamine	T	0·1	*n* 21·5	§
Catechol diacetate	Acetone	D	0·1	*n* 21	§
	Di*iso*butyl ketone	C	0·05	*n* 21	1 : 1
		T	0·1	*n* 22·5	1 : 1; 1 : 2
	Triethylamine	C	0·05	*n* 20·5	1 : 1
		D	0·1	*n* 21	1 : 1
		T	0·1	*n* 22·5	(1 : 1)
Dimethyl terephthalate	Phenol	T	0·1	*n* 18	1 : 4
	Triethylamine	T	0·1	*n* 18	1 : 4
Ethylene glycol diacetate	Acetone	D	0·2	*n* 21	(1 : 1)
	Di*iso*butyl ketone	D	0·2	*n* 21	1 : 1
	Triethylamine	T	0·2	*n* 21	1 : 1
Ethylene glycol dibenzoate	Phenol	T	0·1	*n* 22	1 : 4
	Triethylamine	T	0·1	*n* 20	1 : 4
Ethyl acetate	Acetone	T	0·2	*n* 21	1 : 1
	Azobenzene	T	0·1	*n* 17, 21·9	4 : 1
	1-Naphthol-5-sulphonic acid (oxy-L-acid)	W	0·04	*n* 24	(1 : 1)
	o-Nitrophenol	P	0·1	*n* 20	(1 : 1)
		T	0·1	*n* 14	1 : 1
	p-Nitrophenol sulphuric ester	W	0·04	*n* 24	1 : 1
Ethyl trichloroacetate	Acetone	T	0·2	*n* 20	1 : 1
	Azobenzene	C	0·2	*n* 20	1 : 1; 2 : 1
	Triethylamine	T	0·2	*n* 20	(1 : 1)
α-D-Glucose pentaacetate	Acetone	T	0·1	*n* 21	1 : 1; 1 : 3; 1 : 5
	Aniline	T	0·1	ε, *n* 20	(1 : 1)
	Anisole	T	0·1	ε, *n* 20	(1 : 1)
	Azobenzene	T	0·1	ε, *n* 20, 21	2 : 1; 1 : 1
	Benzoquinone	T	0·1	ε, *n* 20	(2 : 1)
	Diethylamine	T	0·1	ε, *n* 22	(1 : 1)
	o-Nitrophenol	D	0·1	*n* 20	1 : 1
	Phenol	D	0·1	*n* 20	1 : 1; 1 : 6
	Triethylamine	T	0·1	*n* 20, 21	1 : 1
		D	0·1	*n* 20	1 : 1; 1 : 6
Glycerol triacetate	Azobenzene	T	0·1	*n* 20·5	2 : 1
	Di*iso*butyl ketone	T	0·1	*n* 21	1 : 1; (1 : 2 or 1 : 3)
	Diethylamine	D	0·1	*n* 15	(1 : 3)
		T	0·1	*n* 12	1 : 1
	Dioxan	T	0·1	*n* 21·5	1 : 3
	2 : 2′-Dipyridyl	W	0·025	*n* 18·8	(2 : 1)
	4-Hydroxyazobenzene-4′-sulphonic acid	W	0·025	*n* 20·8	§
	1-Naphthol-5-sulphonic acid	W	0·05	*n* 21	(§)
	2-Naphthol-6-sulphonic acid	W	0·05	*n* 24	(§)
	o-Nitrophenol	T	0·1	*n* 21·5	1 : 1
	p-Nitrophenyl sulphuric ester	W	0·04	*n* 17·5, 23	1 : 1
	Pyridine	T	0·1	*n* 20·5	1 : 1
	Sulphanilic acid → 1-naphthol	W	0·01	*n* 22	(§)
	Triethylamine	W	0·2	*n* 20·8	1 : 1; 1 : 3

TABLE 1. (*Continued.*)

Solution: Solutes *a*	*b*	Solvent *	Total molar concn.	Method(s) † and temp.	Mol. ratio ‡ of complex, *a* : *b*
Methyl oxalate	Acetone	C	0·2	*n* 20·5	1 : 1; 1 : 2
	Phenol	D	0·05	*n* 16·5	1 : 2
	Triethylamine	C	0·2	*n* 20·5	1 : 1; 1 : 2
Pentane-1 : 5-diol diacetate	Di*iso*butyl ketone	T	0·1	*n* 21	1 : 2
	Triethylamine	T	0·1	*n* 21	1 : 2
*iso*Propyl acetate	Anisole	D	0·1	*n* 20	1 : 1
	Azobenzene	D	0·1	*n* 19	4 : 1
	Benzoquinone	T	0·2	ε, *n* 20	2 : 1
	3-Methoxybenzanthrone	D	0·01	*n* 20	(2 : 1)
	o-Nitrophenol	D	0·1	*n* 19	1 : 1
		T	0·1	*n* 20	1 : 1; (1 : 2)
	Phenol	T	0·2	ε, *n* 20	1 : 1
Quinol diacetate	Acetone	D	0·1	*n* 21	§
	Di*iso*butyl ketone	C	0·05	*n* 21	(1 : 1); 1 : 2
	Triethylamine	C	0·05	*n* 20·5	(1 : 2)
		D	0·1	*n* 21	1 : 2
Trichloroacetyl chloride	Acetone	C	0·1	*n* 22·5	1 : 1
	Azobenzene	D	0·1	*n* 22	(§)
	Di*iso*butyl ketone	T	0·1	*n* 21	(1 : 1 or 1 : 2)

* Solvents: B = benzene; C = carbon tetrachloride; D = dioxan; EG = ethylene glycol; P = light petroleum (b. p. 80—100°); T = toluene; W = water.
† ε = dielectric constant; *n* = refractive index.
‡ Data in parentheses denote uncertain indications.
§ No evidence of complex formation.

the greater ionisability of the hydrogen atom in the carboxyl group than that in the alcoholic group, and the activity of the methylene group in acetoacetic ester (see also Hughes [4]). The presence of labile hydrogen in some acetates is confirmed by the Rhodamine B test [5] which is positive with alcohol-free pentane-1 : 5-diol diacetate and with glycerol triacetate (though it is negative with ethyl acetate).

The trichloroacetyl chloride–acetone complex detected probably originates in dipole–dipole interaction, at the C=O bond, strongly activated by the trichloro-group. This is the first example of this type of non-hydrogen-bonded complex so far detected by the present means. With bases in non-aqueous solution, trichloroacetyl chloride gives copious precipitates of " Lewis salts."

Chelation in Esters.—If the acetate group is a proton-donor, then weak chelation might be expected between acetate groups in 1 : 2-positions, because a 7-membered chelate ring between them can be formulated. Accordingly, some polyacetylated compounds were examined, and it will be observed (Table 1, Fig. 1) that the compounds containing only two non-adjacent acetyl groups, *e.g.*, the diacetates of pentane-1 : 5-diol or quinol, are bifunctional, but those in which the groups are attached in 1 : 2-positions, *e.g.*, ethylene

TABLE 2. *Physical constants of diacetates of dihydric alcohols and phenols.*

Diacetate of	M. p.	B. p.	Diacetate of	M. p.	B. p.
Catechol	63·5°	—	Quinol	121°	—
Butane-1 : 2-diol	—	196—199°	Butane-1 : 3-diol	—	208°
Butane-2 : 3-diol	—	190(200)	Butane-1 : 4-diol	—	230
Pentane-1 : 2-diol	—	216—217 (219)	Pentane-1 : 5-diol	—	241
Hexane-2 : 3-diol	—	215—220	Hexane-1 : 6-diol	—	260
			Hexane-2 : 5-diol	—	225—230

glycol diacetate, penta-acetylglucose, and glycerol triacetate, can behave monofunctionally, which is consistent with interaction between the 1 : 2-groups. The values of the b. p.s or m. p.s of the recorded compounds of this type (Table 2) are also consistent with this

[4] Hughes, " Ionisation in Organic Chemistry," Roy. Inst. Chem. Lectures, 1955, No. 1.
[5] Lundgren and Binkley, *J. Polymer Sci.*, 1954, **14**, 139, cf. also ref. 6.

suggestion; the 1 : 2-compounds in each case having lower b. p.s or m. p.s than the corresponding ones with the substituent groups more widely separated (cf. the values for di-alcohols and nitro-compounds given in Part IV [6]).

Certain differences in the infrared spectra of the two phenolic diacetates might be attributable to dipole–dipole interaction between the C=O groups, but this appears doubtful and a more likely interpretation is that some form of hydrogen bond is involved. There are differences between the spectra of the diacetates of ethylene glycol and of pentane-1 : 5-diol; these appear to indicate some weak disturbance of the –O– and CH_2 groups in the

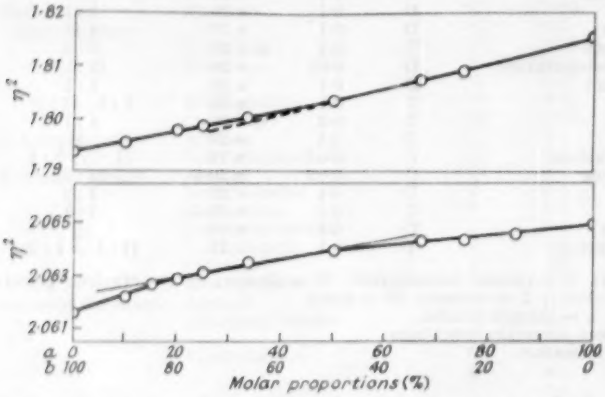
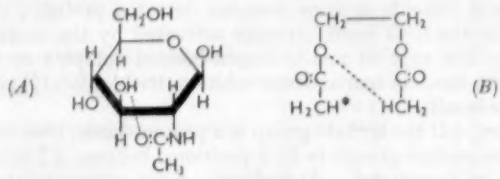


FIG. 2. *Relation between square of refractive index and component ratio in solutions of binary systems.*

Top: *a*, *N*-Acetyl-D-glucosamine; *b*, methanol. Solvent, water.

Bottom: *a*, *N*-Acetyl-D-glucosamine; *b*, methanol. Solvent, ethylene glycol.

ethylene glycol diacetate only, probably owing to hydrogen bonding; there is no evidence of any disturbance of the C=O bond. If a chelate ring involving a hydrogen bond is assumed to be present in ethylene glycol diacetate, it must be 7-membered, and of low energy: it can be broken by phenol, which seems to give a 3 : 1 complex with glycerol



triacetate. This bond, it is suggested, may be formulated as in (*B*). Thus the compound can behave as a monofunctional proton donor, one hydrogen atom (marked *) being available. Details of the infrared spectra are given in the Experimental Section.

Ketones.—No evidence is obtained that any symmetrical ketone can act as an electron acceptor; one isolated test with an unsymmetrical ketone, *viz.*, 2-acetylpyridine, suggests, however, that this compound might do so.

Mechanism of Adsorption of Solutes by Cellulose Acetate, by Chitin, and by Terylene.—(i) *Cellulose acetate.** This material adsorbs many non-ionic polar compounds, *e.g.*, phenols and amines,[7] from water (dispersion or solution) or from non-aqueous solvents; some proton-acceptors, *e.g.*, azobenzene and certain derivatives, are also adsorbed; water-solubilisation by introduction of the sulphato-ester group into a dye molecule does not prevent adsorption, but the introduction of highly ionic groups, *e.g.*, sulphonate groups, usually does prevent it,[8] presumably because the attraction of the substrate is too weak

* The commercial acetate, which is about one-third hydrolysed, has very similar adsorption behaviour to the fully esterified triacetate.

[6] Part IV, Arshid, Giles, and Jain, *J.*, 1956, 559.

[7] Marsden and Urquhart, *J. Textile Inst.*, 1942, **33**, T105.

[8] Vickerstaff, "The Physical Chemistry of Dyeing," Oliver and Boyd, Ltd., Edinburgh, 2nd Edn., 1954.

to overcome that of the water. It will be observed (Table 1) that ethyl acetate and glycerol triacetate form complexes in water with a sulphato-ester; and a sulphonic acid (oxy-L-acid) gives an uncertain indication of combination with ethyl acetate. The following specific adsorption mechanisms for cellulose acetate have been suggested: (*a*) Hydrogen-bonding by acceptance of a proton at the carbonyl oxygen atom of the acetyl group;[7,8] this does not, however, account for adsorption of proton-acceptors. (*b*) Proton-donation by the methyl residues of the acetyl groups.[9] (*c*) Dipole–dipole interaction, not involving hydrogen, between the carbonyl group and the adsorbate molecule.[10] (*d*) Non-polar van der Waals attraction.[11] It seems very probable that adsorption of small solute molecules, *e.g.*, phenol, must be almost entirely due to polar forces, and recent work on cellulose triacetate monolayers [12] suggests that even the larger molecules may be adsorbed largely by polar forces. The present work seems to show that the hydrogen-bonding mechanism (*b*) is more likely than mechanism (*c*) to account for polar attraction. It may in fact be responsible for adsorption even of proton-donors, *e.g.*, phenol, because examination of the hydrogen-bonding properties of a wide variety of compounds has revealed no conclusive evidence that a carbonyl group can form intermolecular hydrogen-bonds in water.[6,13] The –C–H · · · · bond is weak, which is consistent with the general low affinity of solutes for cellulose acetate.

Moore and Russell [14] have used the dielectric-constant method [1] with binary solutions of some cellulose acetate solvents and of some models of this polymer. They detected complexes in hexane between benzyl acetate and chloroform or *m*-cresol, and (in dioxan) between cellobiose α-octa-acetate and aniline or *m*-cresol, but not between benzyl acetate and acetone, dioxan, or pyridine (all in hexane) or between cellobiose octa-acetate and acetone, chloroform, ethyl acetate, or pyridine (all in dioxan). In repetitions of some of these experiments by the present method (solvent: toluene) it is confirmed that benzyl acetate appears not to form a complex with acetone, dioxan, or pyridine.

(ii) *Chitin.* Chitin consists largely of poly-*N*-acetylglucosamine, and adsorption of non-ionic solutes thereon might take place through hydrogen-bonding at the hydroxy- or the acetamido-groups. The behaviour of *N*-acetylglucosamine suggests that in water the hydroxy-groups of chitin are solvent-protected and adsorption takes place by bonding at the acetamido-group. In organic solvents both types of group may be reactive. The results of adsorption experiments with chitin are not inconsistent with this deduction.[15,16]

(iii) *Terylene.* It appears that models of this polymer can act as proton-donors, and a polar mechanism of this nature may therefore be at least partly responsible for adsorption of non-ionic compounds by Terylene (cf. Allingham *et al.*[9]), though for aromatic solutes non-polar attraction between aromatic nuclei in solute and substrate must also operate (cf. refs. 11 and 17).

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[9] Allingham, Giles, and Neustädter, *Discuss. Faraday Soc.*, 1954, **16**, 92.
[10] Majury, *J. Soc. Dyers Col.*, 1954, **70**, 442.
[11] Derbyshire and Peters, *ibid.*, 1955, **71**, 530.
[12] Cameron, personal communication.
[13] Part III, Arshid, Giles, Jain, and Hassan, *J.*, 1956, 72.
[14] Moore and Russell, *J. Appl. Chem.*, 1954, **4**, 369.
[15] Giles, Jain, and Hassan, *Chem. and Ind.*, 1955, 629.
[16] Hassan and Subramanian, personal communications.
[17] Giles, *Discuss. Faraday Soc.*, 1954, **16**, 248.
[18] Cf. Francis, *J. Chem. Phys.*, 1951, **19**, 942.

261. *A Thermodynamic Study of Some Iodine Solutions.*

By W. B. Jepson and J. S. Rowlinson.

The partial pressure, partial molar volume, and solubility of iodine have been measured for solvents with which it forms molecular complexes. All three properties show clearly the effects of the formation of complexes. The partial molar volume at infinite dilution is greatly reduced by such association, the values at 25° varying from 67·9 ml. in *cyclo*hexane to 48·3 ml. in ethyl ether. Measurements of the partial pressure of solid iodine in the presence of the solvent vapours show that small concentrations of complex-forming solvents reduce the iodine concentration in the gas phase. It is suggested that this is due to the formation of a coherent surface phase. Larger concentrations of vapour increase the iodine concentration owing to interaction in the gas phase between iodine and solvent.

The solubility of iodine in organic solvents and the colour of these solutions have long been used to distinguish between substances with which iodine forms molecular complexes and substances to which it is inert. The solutions containing complexes are generally red or brown and the normal solutions violet. The solutions containing complexes show very strong and broad absorption bands in the near-ultraviolet region, which are now generally interpreted as charge-transfer spectra in a binary complex in which the iodine acts as an electron acceptor and the solvent as the donor.[1, 2] Aromatic compounds, ethers, alcohols, and amines have all been found to act as donors. Very weak complexes have been reported between iodine and saturated hydrocarbons,[3] but the effects of these on the physical properties of the solutions are probably negligible. A study of the solubility of iodine in normal solvents was an important part of the work which led Hildebrand to formulate his theory of "regular solutions." He found that such solubilities were always less than ideal by an amount which depended on the energy of vaporisation per unit volume of the solvent.[4] The solubilities in complex-forming solvents, though still less than ideal, were greater than those calculated for a regular solution. However, thermodynamic properties other than solubilities have been little studied, possibly on account of the difficulties of working in conventional apparatus with material which reacts with both mercury and tap-grease. In this paper we report some measurements of the partial pressures and partial molar volumes of iodine in solution and of the partial pressures of solid iodine in the presence of vapours of organic substances at total pressures less than the saturation pressure. The partial pressures were measured in a sealed all-glass apparatus by using radio-iodine to determine the iodine concentration in the vapour phase. The solvents used were *cyclo*hexane, benzene, fluorobenzene, chlorobenzene, bromobenzene, mesitylene, pyridine, ethyl bromide, ethyl iodide, and diethyl ether. All but *cyclo*hexane showed evidence of molecular complexes.

Experimental

Purification of Materials.—Iodine ("AnalaR") was used without further purification, except for the density measurements for which it was finely powdered and stored over phosphoric oxide.

Radioactive iodine, ^{131}I, was obtained from the Radiochemical Centre, Amersham, in 2 mc batches as a carrier-free solution of sodium iodide. This solution was brought to equilibrium with an ethereal solution of normal iodine by 24 hours' shaking. The ether was removed by evaporation in a current of dry air, and the iodine separated from involatile material by vacuum-distillation in a short-path still. The final activity was about 0·25 mc/g.

*cyclo*Hexane (from Messrs. Howards) was freed from aromatic substances by shaking it with a nitrating mixture, then washed with alkali and with water, dried, and fractionally distilled.

[1] Andrews, *Chem. Rev.*, 1954, **54**, 713.
[2] Orgel, *Quart. Rev.*, 1954, **8**, 437.
[3] Evans, *J. Chem. Phys.*, 1955, **23**, 1424.
[4] Hildebrand and Scott, "The Solubility of Non-Electrolytes," Reinhold, New York, 1950.

Benzene (" AnalaR ") was fractionally crystallised three times and dried.

Fluorobenzene, chlorobenzene, and bromobenzene (from British Drug Houses Ltd.) were dried and fractionally distilled.

Mesitylene (from Genatosan Ltd.) was converted into the sulphonic acid, and the crystals were washed with 70% sulphuric acid. The mesitylene was regenerated by refluxing the acid with 15% hydrochloric acid, followed by steam-distillation. It was then dried and fractionally distilled.

Pyridine (" AnalaR ") was dried and fractionally distilled from " Anhydrone."

Ethyl bromide (from British Drug Houses Ltd.) was washed with concentrated sulphuric acid to remove alcohol, with sodium hydrogen carbonate solution, and with water. It was dried and fractionally distilled.

Ethyl iodide (from Messrs. Whiffen) was purified in small batches immediately before use by distillation through a column packed with copper turnings to remove hydrogen iodide, then dried and fractionally distilled.

Ethyl ether (" AnalaR ") was dried and fractionally distilled.

Partial Pressure of Iodine.—The relative concentration of radio-iodine in the vapour phase above a solution of known total iodine concentration was determined by means of a Geiger counter outside, but adjacent to, the glass apparatus. This concentration was compared with that of the vapour from a sample of pure solid iodine prepared from the same batch of radioactive material. The vapour pressure of solid iodine has been measured directly by Gillespie and Frazer.[5] The apparatus, shown schematically in Fig. 1, consisted of a closed circuit of 8 mm. glass tubing connecting the bulb *A* containing the iodine solution, a horizontal tube *B* which enclosed a glass stirrer that was moved magnetically, and an annular vessel *C* which surrounded the Geiger counter *D*. The glass circuit was immersed in two thermostats T_1 and T_2, the temperature of the former being about 3° higher than that of the latter. The parts of the circuit outside the thermostats were heated electrically to a temperature about 10° above that of T_2. A weighed amount of iodine was placed in *A* and the apparatus evacuated. A weighed amount of solvent was then distilled on to the iodine through one of the side-arms near *A*, and the apparatus sealed. The stirrer in *B* caused a rapid mixing of the vapour phase (as shown by its colour) and caused sufficient vibration to keep the liquid in *A* well-mixed. A small correction was applied to the calculated liquid composition to correct for the amounts of solvent and solute which passed into the vapour. The counter and the annular vessel *C* were shielded by 1—2 inches of lead (not shown) from cosmic rays and from direct radiation from the iodine in *A*. Usually over 90% of the observed count-rate was due to vapour in *C*. Once equilibrium had been reached (usually after about 5 hr.) the count-rate was independent of whether or not the vapour was being stirred.

A similar apparatus was used to measure the amount of iodine in the vapour when solid iodine was in contact with the unsaturated vapours of the solvents, but here the solid iodine was in a tube heated to a constant temperature in a vapour-jacket. The original intention was to cover a wider temperature range than could be covered by a liquid thermostat.

Densities of Iodine Solutions.—These were measured under the same conditions and in the same pyknometer as the densities measured by Thacker and Rowlinson.[6]

Solubilities.—Measurements were made by sampling a saturated solution, through a sintered-glass plate, with a small pipette. The whole assembly, including the pipette, was kept for 8 hr. in a thermostat, the temperature of which was measured on a thermometer calibrated by the N.P.L. All solutions were saturated at a temperature about 10° higher than this before being placed in the thermostat. The solution in the pipette was weighed, washed out with carbon tetrachloride, and titrated in triplicate with standard thiosulphate. The method is similar to that of Hildebrand and Jenks.[7] The apparatus was modified for those solutions in ether whose total vapour pressure exceeded atmospheric by using an evacuated and sealed saturator and pipette.

Estimation of iodine in pyridine solution was difficult. Titration with thiosulphate was not possible because of the unfavourable pH, while titration with sodium arsenite gave, at the supposed end-point, a yellow pyridine layer which was not discoloured by excess of arsenite. That this layer contained iodine was shown by acidifying it, for the excess of iodine could then be extracted by carbon tetrachloride. In view of the reported reaction of iodine with pyridine [8]

[5] Gillespie and Frazer, *J. Amer. Chem. Soc.*, 1936, **58**, 2260.
[6] Thacker and Rowlinson, *Trans. Faraday Soc.*, 1954, **50**, 1036.
[7] Hildebrand and Jenks, *J. Amer. Chem. Soc.*, 1920, **42**, 2180.
[8] Kleinberg, Colton, Sattizahn, and VanderWerf, *ibid.*, 1953, **75**, 442.

this chemical method was abandoned and the iodine concentration determined, in freshly made solutions, by using radio-iodine as a tracer.

The solubility of iodine in iodobenzene could not be measured, as the mixture apparently reacted chemically, depositing lemon-yellow crystals.

The reproducibility of the solubilities was better than 1%, but for pyridine solutions there must be some doubt as to the chemical state of the dissolved iodine.

Heat of Dilution.—Only in one solvent, ethyl iodide, was the solubility at 25° great enough for a determination of the heat of dilution. This was measured in a calorimeter similar to that of Thacker and Rowlinson [6] except that their U-tube containing mercury was replaced by two coaxial tubes, the inner of which contained the solution and the outer the solvent. The inner tube was sealed by a microscope cover-slide held in place by a trace of Silicone grease until the mixing took place, by inverting the calorimeter, the cover-slide being then broken by a glass bead in the inner tube.

Results

Partial-pressure Measurements.—The solvents used in these measurements were *cyclo*hexane, benzene, fluorobenzene, and mesitylene at 55·3°, and diethyl ether at 35·0°, 45·0°, and 55·3°. Ethyl iodide was not used because of the possibility of exchange with the radio-iodine.

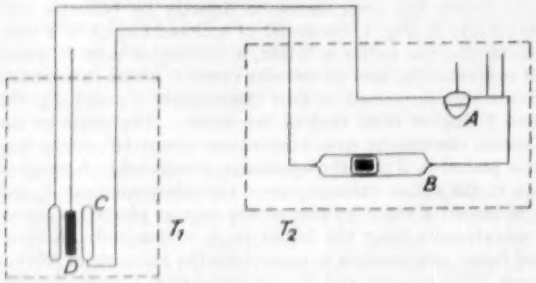


Fig. 1. *Apparatus used for partial-pressure measurements.*

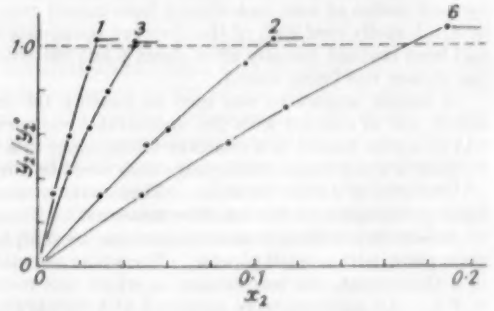


Fig. 2. *Relative concentration of iodine in the vapour phase above liquid solutions at 55·3° for the solvents,* cyclo*hexane* (1), *benzene* (2), *fluorobenzene* (3), *and mesitylene* (6).

The results are shown in Figs. 2 and 3. The function $(y_2/y_2°)$ is the ratio of the mole fraction of iodine in the vapour phase to the mole fraction in a vapour mixture containing the same concentration as the vapour from pure solid iodine. This function is plotted against x_2, the mole fraction of the iodine in the liquid phase. In every solution the highest value of x_2 is that corresponding to saturation. These measurements were made on solutions containing excess of solid iodine.

The amount of iodine in the vapour phase when solid iodine is in equilibrium with unsaturated vapours is shown in Figs. 4 and 5 for air and for the vapours of *cyclo*hexane, benzene, fluorobenzene, pyridine, and ether at 56°. The function $(y_2/y_2°)$ is here plotted against the pressures of the added vapours, which are assumed to be perfect.

Density Measurements.—Fig. 6 shows V_2' the apparent molar volume of iodine in liquid solutions at 25°, defined by

$$V_2' = (v - v_1)/n_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

FIG. 3. *Relative concentration of iodine in the vapour phase above liquid solutions of ethyl ether* (10) *at, from left to right,* 35·0°, 45·0°, *and* 55·3°.

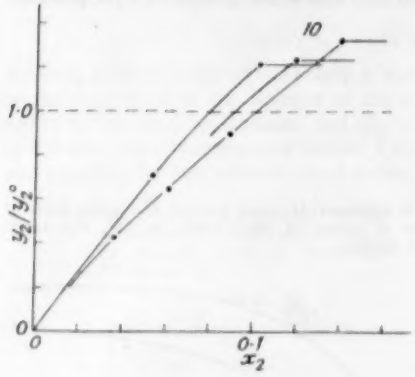


FIG. 4. *Relative concentration of iodine in the vapour phase for solid iodine at* 56° *in the presence of the vapours of* cyclo*hexane* (1), *benzene* (2), *and fluorobenzene* (3).

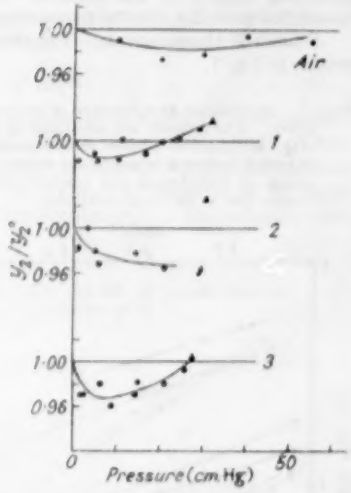


FIG. 5. *Relative concentration of iodine in the vapour phase for solid iodine in the presence of ethyl ether vapour at* 56°. *Measurement at* 35° *gave very similar results.*

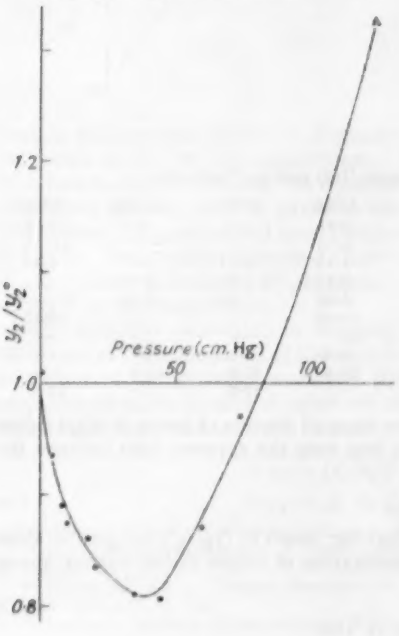
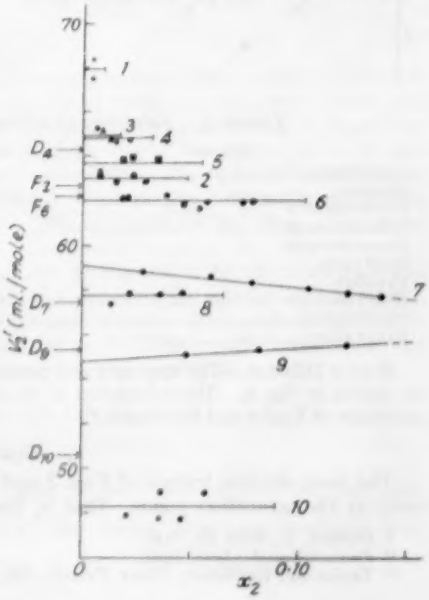


FIG. 6. *Apparent molar volume of iodine at* 25° *in solutions of* cyclo*hexane* (1), *benzene* (2) (●), *fluorobenzene* (3) (▲), *chlorobenzene* (4) (●), *bromobenzene* (5) (■), *mesitylene* (6), *pyridine* (7), *ethyl bromide* (8), *ethyl iodide* (9), *and ethyl ether* (10). *The arrows show the values of* V_2' *at high dilution as observed by Dawson* (*D*) *and Fairbrother* (*F*) *for solvents* 2, 4, 6, 7, 9, *and* 10.



where v is the volume of a solution containing n_1 moles of solvent and n_2 of solute, and v_1 is the volume of n_1 moles of pure solvent. At infinite dilution, and at other concentrations if V_2' is independent of concentration, the apparent molar volume is the same as the partial molar volume. The accuracy of V_2' increases with the concentration and varies inversely with the molecular weight of the solvent. The values obtained agree moderately well with those calculated from the density measurements at higher dilutions by Dawson [9] and Fairbrother.[10]

Solubility Measurements.—The results are set out in Table 1 and compared with previous results in Fig. 7.

FIG. 7. *Solubilities as a function of temperature. The solvents are numbered as in Fig. 6. Circles denote measurements reported here and triangles the measurements of Hildebrand and others.[6] The broken line is the ideal solubility.*

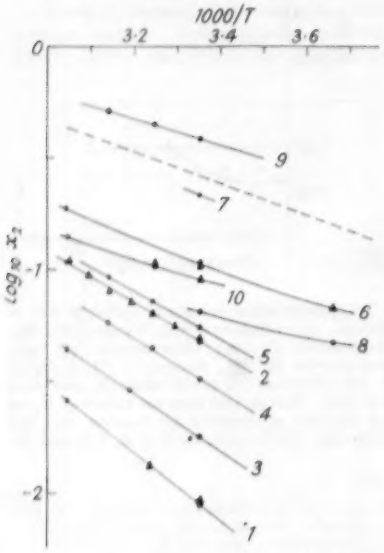


FIG. 8. *The apparent, H_2', and partial, $\overline{H}_2$, molar heats of dilution of iodine in ethyl iodide at 25°, relative to infinite dilution.*

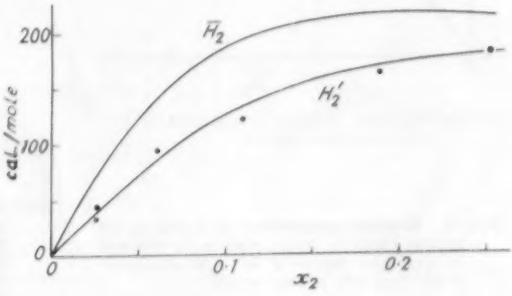


TABLE 1. *Solubility of iodine in moles/100 moles of solution.*

Solvent	0·00°	24·96°	35·07°	45·08°	55·33°
*cyclo*Hexane	—	0·91	—	—	2·69
Benzene	—	4·75	—	—	10·78
Fluorobenzene	—	1·73	2·77	—	4·45
Chlorobenzene	—	3·19	4·40	5·75	—
Bromobenzene	—	5·50	7·15	9·34	—
Mesitylene	—	10·82	—	—	19·15
Pyridine	—	21	—	—	—
Ethyl bromide	4·72	6·50	—	—	—
Ethyl iodide	—	32·8	37·9	41·7	—
Ethyl ether	—	—	10·2	—	14·0

Heat of Dilution.—The apparent and partial molar heats of dilution of iodine in ethyl iodide are shown in Fig. 8. The calculation of the partial heat from the apparent heat followed the procedure of Taylor and Rowlinson.[11]

DISCUSSION

The most obvious feature of Figs. 2 and 3 is that the values of (y_2/y_2°) are greater than unity at the saturation point. That is, the concentration of iodine in the vapour above

[9] Dawson, *J.*, 1910, **97**, 1041.
[10] Fairbrother, *J.*, 1948, 1051.
[11] Taylor and Rowlinson, *Trans. Faraday Soc.*, 1955, **51**, 1183.

these solutions is greater than that in the vapour of pure solid iodine. Such an increase in concentration is most naturally interpreted as a consequence of the departure of the vapour mixture from the perfect-gas laws. (The departure of the vapour of pure solid iodine may be neglected owing to the low total pressure.) Similar increases have been observed, although generally at higher total pressures, for many other systems in which a gas is in contact with a slightly volatile solid or liquid.[12] It has been shown that the logarithm of the ratio (y_2/y_2°) may be expressed by a series of which the first two terms are [13]

$$\ln (y_2/y_2^\circ) = \ln a_2 + p\,(V_s - 2B_{12})/RT \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where a_2 is the activity of the solute in the condensed phase (solid or solution) with respect to the pure solid in the absence of the first component; V_s is the molar volume of the solute in the condensed phase, and B_{12} is the second virial coefficient for the interaction in the gas phase between component 1 and component 2. This coefficient must be large and negative for the interaction of iodine with solvent molecules and is undoubtedly the

FIG. 9. *The virial coefficient for the interaction of iodine and ethyl ether. (▲ from the results of Brüll and Ellerbrock.*[17])

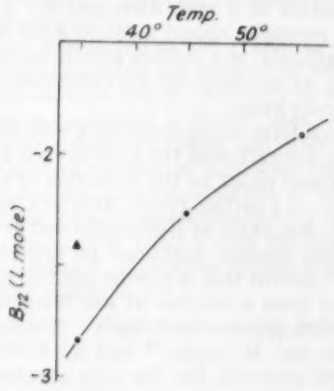
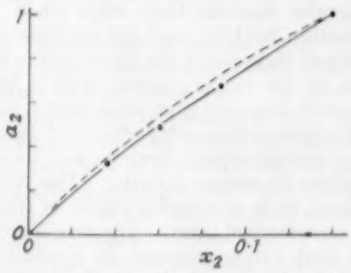


FIG. 10. *The activity of iodine in ether solution at 55·3°.*



The full line is calculated from equation 4 and the broken line from equation 3. The relative positions of these lines are very similar for the other solutions.

term in this equation by virtue of which (y_2/y_2°) exceeds unity above a saturated solution, for which $a_2 = 1$ at true equilibrium. The activity of iodine in the liquid phase may therefore be calculated from this equation at all concentrations by correcting $\ln (y_2/y_2^\circ)$ by a constant amount, as p is virtually independent of the iodine concentration in the gas. The values of B_{12} calculated from this equation for the iodine–ether interaction are shown in Fig. 9. These values indicate a considerable degree of interaction between the molecules. B_{12} is -2800 ml./mole at 35°, compared with -1000 ml./mole for the ether–ether interaction [14] at this temperature.

The activities calculated in this way are shown in Fig. 10 as functions of x_2. The curvature of these graphs is of the sign to be expected for a regular solution, for which the logarithm of the activity coefficient (referred to unit activity in the ideal solution) is proportional to the square of either the mole fraction or, in Hildebrand's formulation, the volume fraction of the solvent. These proportionalities lead directly to:

$$\ln a_2 = (x_1/x_1^s)^2 \ln (x_2^l/x_2^s) + \ln (x_2/x_2^l) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$\ln a_2 = (\phi_1/\phi_1^s)^2 \ln (x_2^l/x_2^s) + \ln (x_2/x_2^l) \quad . \quad . \quad . \quad . \quad . \quad (4)$$

[12] *E.g.*, Diepen and Scheffer, *J. Amer. Chem. Soc.*, 1948, **70**, 4085; Webster, *Proc. Roy. Soc.*, 1952, *A*, **214**, 61.
[13] Robin and Vodar, *Discuss. Faraday Soc.*, 1953, **15**, 233; Ewald, Jepson, and Rowlinson, *ibid.*, p. 238; Bell, *ibid.*, p. 290.
[14] Lambert, Roberts, Rowlinson, and Wilkinson, *Proc. Roy. Soc.*, 1949, *A*, **196**, 113.

where ϕ is the volume fraction, the superscript i denotes ideal, the superscript s denotes saturation, and the state of unit activity is the saturated solution. Fig. 10 shows that the second of these equations fits the experimental results more closely than the first.

The second virial coefficient B_{12} can be measured by studying the amount of iodine in the gas phase when solid iodine is in contact with the vapours of the solvents, provided that the activity of the solid iodine is not affected by the added vapour. If a_2 is independent of p, then $\ln (y_2/y_2^\circ)$ [and therefore (y_2/y_2°) at low p] will be a linear increasing function of p. The results recorded in Figs. 4 and 5 show that this is not so. In every case a small amount of added vapour decreases the concentration of iodine in the gas phase. This diminution was quite stable and reproducible, although the accuracy of (y_2/y_2°) was no better than $\pm 1\%$. The addition of air in the range 100—600 mm. Hg caused a slight decrease of up to 2%. *cyclo*Hexane vapour caused a similar initial fall but (y_2/y_2°) then increased and was greater than unity for pressures greater than 200 mm. If the curve is extrapolated it passes through the value of (y_2/y_2°) obtained from the saturated liquid solutions. The other vapours decreased the iodine concentration at 56° by the following amounts: benzene (4%), fluorobenzene (4%), and ethyl ether (18%). The extrapolated curves pass through the value of (y_2/y_2°), except for that of benzene—an exception for which we cannot account but which is probably an experimental error. Pyridine was found to cause a much greater decrease than ethyl ether. The addition of 5 mm. decreased the iodine concentration by 18%, and the addition of higher pressures caused a yellow solid to be precipitated throughout the apparatus. Acetone, ethanol, and methyl acetate appeared to react, for the iodine concentration in the vapour, as measured by the count-rate, rose steadily with time and gave no signs of reaching a steady value.

It is apparent that ethyl ether and pyridine, which form strong complexes with iodine, and, to a smaller extent, benzene and fluorobenzene, interact with the solid in such a way as to reduce its surface activity. This interaction could either be the formation of a new solid phase, such as mixed crystals, or the formation of a surface phase, such as a tightly bound, chemisorbed layer. The first is probably the less likely as Hildebrand and Jenks [7] showed that iodine prepared by crystallisation from benzene contained no appreciable amount of solvent, and Harris, Mack, and Blake [15] showed that a powder photograph of iodine prepared by very rapid evaporation of ether from a solution at low temperature showed no unusual features. The second explanation appears more likely. The results may be compared with those obtained by Wright and McGregor [16] and by Brüll and Ellerbrock.[17] The former used both static and flow methods, but the only quantitative result they give is a fall in the iodine concentration of 3% on the addition of air at atmospheric pressure. This agrees well with our figure. In their flow measurements they found that the organic vapours initially carried over more iodine than air but that the amount fell with time and eventually was less than that carried by air. Brüll and Ellerbrock used a flow method and found increases in the amount of iodine carried over. From their results with ethyl ether a figure of B_{12} has been calculated which is shown in Fig. 9. Neither of these sets of results is inconsistent with those reported here, for with a flow technique the problem becomes one of kinetics rather than of equilibrium measurement. The amount carried over will depend on the relative rates of the formation of the surface film and of its removal by evaporation.

The values of $(-B_{12})$ shown in Fig. 9 are therefore only minimum values. The actual values may be greater if the surface phase persists in the saturated liquid solution. At much higher pressures Braune and Strassman [18] demonstrated a considerable increase in iodine concentration in the presence of carbon dioxide, a substance which is unlikely to form a strongly adsorbed layer.

The partial molar volumes at infinite dilution (Fig. 6) show the effect of complex formation most clearly. The solvents may be arranged in order of decreasing molar volume of iodine at 25°, as follows: *cyclo*hexane (67·9 ml.), fluorobenzene (65·0 ml.), chlorobenzene

[15] Harris, Mack, and Blake, *J. Amer. Chem. Soc.*, 1928, **50**, 1583.
[16] Wright and McGregor, *J.*, 1929, 1364.
[17] Brüll and Ellerbrock, *Z. anorg. Chem.*, 1934, **216**, 353.
[18] Braune and Strassman, *Z. phys. Chem.*, 1929, **143**, 225.

(64·9 ml.), 1 : 4-dioxan (64·7 ml.), bromobenzene (63·6 ml.), benzene (63·0 ml.), *p*-xylene (62·2 ml.), mesitylene (62·0 ml.), pyridine (59·1 ml.), iodine (59 ml.), ethyl bromide (57·8 ml.), ethyl iodide (54·8 ml.), ethyl ether (48·3 ml.). The figure for iodine, as solvent, is that obtained by extrapolation [4] of the density of liquid iodine to 25°, and the figures for dioxan and xylene are from measurements by Fairbrother.[10] The range covered by these volumes is surprisingly high. It is clear that in solvents in which there is little or no complex formation the volume of the iodine is greater than in liquid iodine. There is evidence that liquid iodine itself is not a normal liquid held together only by van der Waals forces. It has an appreciable electrical conductivity which decreases with temperature [19] and may be due to an electron-transfer equilibrium,* such as :

$$2I_2 = I^+ + I_3^-$$

Thus, if the volume in *cyclo*hexane is taken as the normal volume, it follows that the formation of complexes is accompanied by a diminution of volume in every case, including that of liquid iodine itself. The position of iodine, as solvent, in this list explains Ham's observation [20] that "it seems possible that the change of volume on complexing is negative even though the volume of mixing is positive." He found the volume change for the formation of one mole of complex to be −1·5 ml. in benzene and −3·3 ml. in mesitylene, by observing the effect of pressure on the equilibrium constant, as measured spectroscopically.

The solubilities at 25° (Table 1) show that the decrease in partial molar volume is roughly parallel to the increase in solubility. The solubility in ethyl ether and in ethyl iodide confirms the great ability of these solvents to form complexes. In ethyl iodide, where the solubility is greater than ideal, the formation of complexes has been confirmed spectroscopically by Keefer and Andrews,[21] and in ethyl ether by Benesi and Hildebrand.[22] The heat of solution at saturation (the so-called last heat of solution) may be calculated from the temperature coefficient of the solubility after applying a small correction for the variation of activity coefficient with concentration.[23] The results for four of the solutions are compared in Table 2 with the heats of solution measured calorimetrically by Hartley and Skinner.[24] The latter include a small but unknown heat of dilution, so the agreement is quite satisfactory.

TABLE 2. *Heat of solution,* (1) *from solubility and* (2) *measured directly,*[24] *in kcal./mole.*

Solvent	(1)	(2)	Solvent	(1)	(2)
*cyclo*Hexane	6·5	5·8	Benzene	4·4	4·25
Chlorobenzene	4·8	4·75	Ethyl ether	1·4	1·8

Hartley and Skinner have already pointed out the relation between the heat of solution and the complex-forming power of the solvent.

In conclusion, the measurements reported here on iodine solutions and on the equilibrium between solid iodine and organic vapours show that the formation of donor–acceptor complexes affects many of the physical properties, and that any of these properties may be used to place solvents roughly in the order of complex-forming power. In increasing power, the best order is probably paraffins, halogenobenzenes, benzene, (toluene), xylenes, mesitylene, ethyl bromide, ethyl ether and pyridine, ethyl iodide. This order agrees in the main with others based on spectroscopic measurements of the equilibrium constant of the association.[1, 2, 25]

One of us (W. B. J.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

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* We are indebted to Dr. F. Fairbrother for this suggestion.

[19] Rabinovitsch, *Z. phys. Chem.*, 1926, **119**, 79.
[20] Ham, *J. Amer. Chem. Soc.*, 1954, **76**, 3881.
[21] Keefer and Andrews, *ibid.*, 1952, **74**, 1891.
[22] Benesi and Hildebrand, *ibid.*, 1949, **71**, 2703.
[23] Williamson, *Trans. Faraday Soc.*, 1944, **40**, 421.
[24] Hartley and Skinner, *ibid.*, 1950, **46**, 621.
[25] Kortum and Vogel, *Z. Electrochem.*, 1955, **59**, 16.

262. *Kinetics of the Depolymerisation of Trioxan in Aqueous Acids, and the Acidic Properties of Aqueous Hydrogen Fluoride.*

By R. P. Bell, K. N. Bascombe, and J. C. McCoubrey.

Measurements have been made of the rate of depolymerisation of trioxan at 25° in concentrated aqueous solutions of hydrochloric, perchloric, sulphuric, and hydrofluoric acids, together with the acidity functions (obtained from indicator measurements) of aqueous hydrofluoric acid up to 43 per cent. by weight. For all the catalyst solutions used the rate of depolymerisation is more closely related to the acidity function of the solution than to its concentration, thus indicating that the transition state of the reaction does not involve a water molecule. Although hydrofluoric acid is a weak acid in dilute solution, its acidity increases rapidly with concentration in the range 5—15M, and in the most concentrated solutions it simulates the behaviour of a strong acid. It is shown that this can be accounted for in terms of the successive formation of the species HF_2^-, $H_2F_3^-$, and $H_3F_4^-$.

It has been previously shown [1] that the depolymerisation of paraldehyde in aqueous solutions of strong acids is a first-order reaction whose velocity is closely related to the acidity function of the acid solution. The present paper reports a similar study of the depolymerisation of the related substance trioxan (trioxymethylene). This reaction has previously been investigated by Skrabal, Stockmair, and Schreiner,[2] who used as catalyst only toluene-*p*-sulphonic acid at a single concentration, and also by Walker and Chadwick,[3] who studied a limited range of concentrations of phosphoric acid at 40°. Paul [4] showed that Walker and Chadwick's results could be correlated with the acidity functions of the catalyst solutions, and the same author demonstrated a similar correlation for the rate of depolymerisation in mixtures of perchloric acid and perchlorates.[5] However, the concentration range covered is small, and most of the kinetic results refer to 40°, while the acidity functions were measured at room temperature.

The catalysts studied in the present investigation include aqueous hydrogen fluoride up to 50 per cent. by weight. In dilute aqueous solutions hydrofluoric acid is a weak acid, and the presence of the bifluoride ion does not cause any complications in the catalytic behaviour of these solutions.[6] On the other hand, anhydrous hydrogen fluoride is one of the most strongly acidic media known, and it is therefore of interest to follow the change in acid properties with change of concentration. In addition to the kinetic measurements, the acidity functions of aqueous hydrogen fluoride solutions have been measured by means of indicators.

Experimental

A commercial sample of trioxan (Eastman Organic Chemicals) was used without further purification. It gave no detectable free formaldehyde on dissolving in water, and when set aside overnight with 50 per cent. sulphuric acid produced more than 99% of the theoretical quantity of formaldehyde, as estimated by the method described below. The solutions of hydrochloric, perchloric, and sulphuric acids were made from "AnalaR" reagents, and were titrated with sodium hydroxide solution which had been standardised against constant-boiling hydrochloric acid. Solutions of hydrofluoric acid in the range 40—60% were made by passing hydrogen fluoride gas from a cylinder into the "AnalaR" acid. All solutions containing hydrofluoric acid were kept in Polythene vessels. Acid concentrations are expressed throughout in moles per litre of solution, the percentage of hydrogen fluoride by weight being also given for the solutions of this acid.

In the kinetic experiments, 1—3 g. of trioxan were dissolved in 50 c.c. of the acid solution at 25°, and the reaction was followed by estimating formaldehyde at intervals in 5 c.c. samples.

[1] Bell and Brown, *J.*, 1954, 774.
[2] Skrabal, Stockmair, and Schreiner, *Z. phys. Chem.*, *A*, 1934, **169**, 177.
[3] Walker and Chadwick, *Ind. Eng. Chem.*, 1947, **39**, 974.
[4] Paul, *J. Amer. Chem. Soc.*, 1950, **72**, 3813.
[5] *Idem*, *ibid.*, 1952, **74**, 141.
[6] Bell and McCoubrey, *Proc. Roy. Soc.*, 1956, *A*, **234**, 192.

The sample was added to a known excess of N/10- or N/100-iodine solution, and an excess of 2N-sodium hydroxide solution added immediately. After 10—30 minutes (to complete the oxidation of the formaldehyde to formic acid), the solution was acidified with 2N-hydrochloric acid, and the unchanged iodine titrated with N/10- or N/100-sodium thiosulphate solution. In most of the experiments less than 10% of the total reaction was followed, so that no evidence was obtained as to the order of the reaction. However, in the more concentrated solutions of hydrofluoric acid the course of the reaction was accurately of the first order over more than 75% depolymerisation : further, the reaction velocity was proportional to the trioxan concentration over a three-fold range. The first-order velocity constants were obtained from a plot against time of $\log_{10}$ [trioxan], or, for the slowest reactions, by plotting [formaldehyde] against time and dividing the slope of this line by the initial trioxan concentration. The initial formaldehyde content of the trioxan solutions was negligible, but in some experiments the first one or two titres (corresponding to $<0.5\%$ of the reaction) showed a slightly more rapid formaldehyde production than the remainder of the reaction. This may be due to the presence in the trioxan of a very small amount of a less stable polymer of formaldehyde, conceivably the less stable conformation of trioxan itself.

TABLE 1. *Depolymerisation of trioxan at 25°.*

c = acid concentration, mole/l. of solution. k = first-order velocity constant (sec.$^{-1}$)

Hydrochloric acid

c	0·0469	0·0778	0·0798	0·220	0·375	0·590	0·755	0·960	1·17
10^5k ...	0·218	0·238	0·275	0·636	1·38	2·67	4·02	6·11	7·75
H_0	+1·42	+1·17	+1·16	+0·67	+0·42	+0·20	+0·08	−0·04	−0·17
c	1·41	1·62	1·75	1·99	2·32	2·70	2·82	3·03	3·27
10^5k ...	10·5	13·7	15·1	22·1	32·4	50·9	55·6	68·1	91
H_0	−0·29	−0·39	−0·44	−0·54	−0·67	−0·82	−0·86	−0·93	−1·02
c	3·50	3·64	3·70	3·81	3·96	4·46	4·92	5·40	5·92
10^5k ...	112	131	132	154	178	283	410	603	1070
H_0	−1·10	−1·15	−1·17	−1·21	−1·26	−1·44	−1·60	−1·77	−1·95

Perchloric acid

c	0·765	1·00	1·24	1·50	1·78	2·23	2·81	3·26	3·75
10^5k ...	3·78	6·22	8·61	14·7	19·3	34·4	75·0	130	262
H_0	+0·08	−0·12	−0·27	−0·44	−0·56	−0·76	−1·01	−1·22	−1·46
c	4·19	4·23	4·93	5·14					
10^5k ...	384	503	1340	2040					
H_0	−1·67	−1·69	−2·07	−2·20					

Sulphuric acid

c	0·260	0·360	0·488	0·760	1·00	1·28	1·48	2·09	2·42
10^5k ...	1·12	1·73	2·64	4·42	6·64	10·4	13·2	33·3	47·9
H_0	+0·54	+0·39	+0·26	+0·03	−0·13	−0·30	−0·41	−0·75	−0·92
c	2·56	3·05	3·48	4·00	4·59				
10^5k ...	59·0	117	197	356	673				
H_0	−0·99	−1·25	−1·45	−1·68	−1·95				

Hydrofluoric acid

%HF	1·44	1·80	2·55	3·91	6·81	8·36	12·4	151	15·5	26·9	30·2
c	0·72	0·91	1·30	2·06	3·50	4·61	6·60	7·95	8·20	14·9	16·9
10^5k ...	0·17	0·19	0·24	0·63	1·15	1·65	4·4	6·9	8·6	70	192
H_0 ...	+1·39	+1·33	+1·25	+1·00	+0·58	+0·48	+0·20	+0·02	−0·02	−0·87	−1·10
%HF	31·0	33·2	36·9	39·2	43·5	48·5	48·8	51·6	53·7	53·8	
c	17·4	18·9	21·2	22·7	25·5	29·6	29·8	31·0	32·6	32·8	
10^5k ...	198	339	870	2300	6590	28,200	30,400	85,700	205,000	223,000	
H_0 ...	−1·16	−1·33	−1·62	−1·81	−2·15	—	—	—	—	—	

The acidity functions given in Table 1 for hydrochloric, sulphuric, and perchloric acids are interpolated from the results of Hammett and his co-workers.[7] Those for hydrofluoric acid are interpolated from our own measurements, which are recorded in Table 2 and shown graphically in Fig. 1. These were made with a Hilger " Spekker " photoelectric absorptiometer, the mercury line 3650 Å being used for the indicator *p*-nitroaniline, and the 4047 Å line for *o*-nitroaniline and 4-chloro-2-nitroaniline. The solutions were made up in a poly(vinyl chloride) weighing bottle, brought to 25°, and transferred for measurement to a cell constructed by

[7] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827.

TABLE 2. *Acidity functions of aqueous hydrogen fluoride at 25°.*

Indicator, p-*nitroaniline*; pK = 1·11

%HF	2·07	2·17	2·72	2·80	4·66	7·97	9·81	11·1	12·1	13·7	15·0	17·5
c	1·07	1·12	1·40	1·44	2·43	4·10	5·12	5·65	6·30	7·20	7·95	9·35
H_0 ...	+1·33	+1·26	+1·23	+1·11	+0·90	+0·50	+0·38	+0·27	+0·23	+0·09	+0·04	−0·19

Indicator, o-*nitroaniline*; pK = −0·15

%HF	15·1	17·5	22·7	25·3	31·3	33·7	37·1
c	8·00	9·35	12·4	14·0	17·6	19·2	21·3
H_0 ...	−0·03	−0·18	−0·58	−0·82	−1·09	−1·38	−1·65

Indicator, 4-*chloro*-2-*nitroaniline*; pK = −0·91

%HF	32·8	38·9	40·8	42·7
c	18·6	22·5	23·7	25·0
H_0 ...	−1·38	−1·71	−1·97	−2·10

cementing together Perspex sheet with a solution of Perspex in dichloroethylene. Measurements were made as rapidly as possible, and the cell was washed out immediately after use. In this way it could be used a number of times without appreciable optical deterioration, though a check was made by measuring the optical density of the cell filled with water before and after each measurement with acid. The values of the acidity function H_0 were calculated in the usual way, using the pK values given by Hammett[7] for the three indicators.

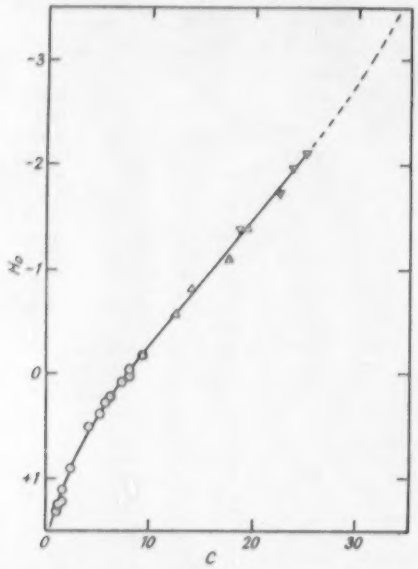


FIG. 1.
○, *p*-Nitroaniline.
△, *o*-Nitroaniline.
▽, 4-Chloro-2-nitroaniline.

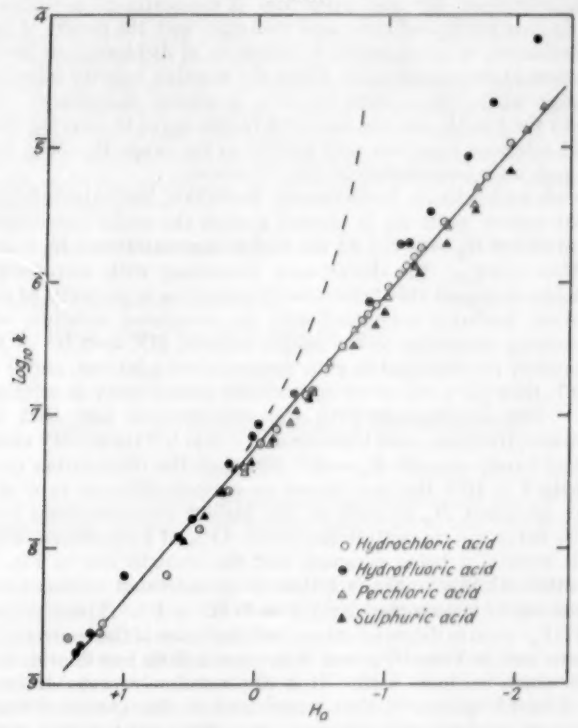
DISCUSSION

Like the analogous reaction of paraldehyde,[1] the depolymerisation of trioxan shows a close relation between the reaction velocity and the acidity function of the catalyst solution. This is shown by Fig. 2, in which $\log_{10}k$ is plotted against H_0. There are small systematic deviations between the results for hydrochloric, perchloric, and sulphuric acids, but on the whole the results are well represented by the straight line drawn in the diagram, which has a slope of 1·2. The broken line in Fig. 2 represents the result of plotting $-\log_{10}c$ in place of H_0 for the experiments with hydrochloric acid. Similar curved plots are obtained for the other strong acids, and it is clear that the reaction velocity follows the acidity function much more closly than it does the acid concentration.

The conclusion to be drawn from this is that in the depolymerisation of trioxan in aqueous solution no water molecule is included in the transition state. The same

conclusion had been reached for the depolymerisation of paraldehyde, and there is the further parallel that both reactions can take place as uncatalysed, homogeneous, gas reactions,[8] as acid-catalysed, heterogeneous, gas reactions, and also as acid-catalysed reactions in non-hydroxylic solvents.[9] No water molecules are available under these conditions, and it is also interesting to note that trioxan can be depolymerised by passing its vapour over a sulphonic acid resin catalyst,[10] and paraldehyde by shaking a toluene

FIG. 2.



solution with an " acidic " alumina–silica catalyst.[11] There is a close analogy between the depolymerisation reactions and the hydrolysis of methylal, for which there is again a parallelism between reaction velocity and acidity function.[12] Although a water molecule is of course ultimately involved, the rate-determining step is believed to be $CH_2(OMe)\cdot\overset{+}{O}HMe \longrightarrow CH_2{:}\overset{+}{O}Me + MeOH$, the corresponding step in the trioxan depolymerisation being :

All these reactions give a slope somewhat greater than unity for the plot of $\log_{10} k$ against H_0. This may be associated with the presence of several equivalent oxygen atoms in these

[8] Bell and Burnett, *Trans. Faraday Soc.*, 1938, **34**, 420.
[9] *Idem, ibid.*, 1939, **35**, 474.
[10] Schnizer, Fisher, and Maclean, *J. Amer. Chem. Soc.*, 1953, **75**, 4347.
[11] T. Spencer, unpublished work in this laboratory.
[12] McIntyre and Long, *J. Amer. Chem. Soc.*, 1954, **76**, 3240.

molecules, thus allowing the attachment of more than one proton, but it more probably arises from the limitations inherent in the concept of the acidity function as a universally valid measure of acidity. Thus, it may be noted that all these reactions involve the attachment of a proton to an oxygen atom, while the indicators used in measuring H_0 are nitrogen bases.

The results for hydrofluoric acid also fit the plot of Fig. 2, although in dilute aqueous solution it is a weak acid with a dissociation constant of about 7×10^{-4}. There is little information available about the acid properties of concentrated solutions of weak acids, but the present finding for hydrofluoric acid contrasts with the results of Bell and Brown [1] for the depolymerisation of paraldehyde in solutions of dichloroacetic and trichloroacetic acids, and of sodium hydrogen sulphate, where the reaction velocity increased with concentration in a range where the acidity function is almost stationary. However, in the present work both the kinetic and the indicator results agree in showing that the acidity of hydrofluoric acid solutions increases very rapidly in the range 10—50% by weight, and it is of interest to seek an interpretation of this behaviour.

The strong acids hydrochloric, hydrobromic, perchloric, and sulphuric (first dissociation) give very similar curves when H_0 is plotted against the molar concentration, c, at least up to acidities of about $H_0 = -2$. At the higher concentrations H_0 is numerically very much greater than $-\log_{10}c$, the discrepancy increasing with increasing concentration. It seems reasonable to regard this behaviour primarily as a property of the hydrogen ion in aqueous solution, probably connected with the associated structure of water. For a weak acid dissociating according to the simple scheme, $HX \rightleftharpoons H^+ + X^-$, the value of $[H^+]$ is approximately proportional to $c^{\frac{1}{2}}$ in concentrated solutions, and if the dissociation constant $K < 0{\cdot}1$, then $[H^+]$ will never appreciably exceed unity in solutions of attainable concentrations. This corresponds with the experimental fact that in concentrated solutions of dichloro-, trichloro-, and trifluoro-acetic acid [1,13] the acidity varies little with the concentration and barely exceeds $H_0 = 0$. Although the dissociation constant of hydrofluoric acid is only 7×10^{-4}, this acid shows an entirely different type of behaviour, and the acidity rises to about $H_0 = -3{\cdot}3$ at the highest concentrations studied. (In Fig. 1 the part of the curve for concentrations above 43% of hydrofluoric acid is constructed from the kinetic results, it being assumed that the straight line in Fig. 2 can be extrapolated.) We attribute this to the fact that in concentrated solutions its dissociation is not even approximately represented by $HF \rightleftharpoons H^+ + F^-$. There is good evidence for the existence of HF_2^- even in dilute solutions, and the value of the constant $[HF_2^-]/[HF][F^-] = 3{\cdot}97$ (cf. Broene and de Vries [14]) means that there is little free fluoride ion present in any of the solutions which we have used. It is also extremely probable (and supported by evidence from infrared spectra [15]) that larger ions of the general formula $H_{n-1}F_n^-$ are present in the more concentrated solutions, since there exist several series of solid acid fluorides, such as KHF_2, KH_2F_3, KH_3F_4, and KH_4F_5. On the other hand, it is unlikely that polymers of undissociated hydrogen fluoride exist to an appreciable extent in aqueous solutions, though they do so in the vapour. There is no evidence for the presence of H_2F_2 in aqueous solutions known to contain HF_2^- and H^+, and it is commonly described as a strong acid. This can be ascribed to the spread of the negative charge over the two fluorine atoms in the species HF_2^-, thus stabilising the anion relative to the undissociated acid, and the same argument will apply to the ions $H_2F_3^-$, $H_3F_4^-$, etc.

The observed variations of acidity with concentration can be explained along these lines. Suppose for simplicity that one ion, $H_{n-1}F_n^-$, predominates over a certain concentration range. The equilibrium governing the hydrogen ion concentration is then $nHF \rightleftharpoons H^+ + H_{n-1}F_n^-$, and we have approximately $[H^+] \propto [HF]^{n/2}$. If $n > 2$, $[H^+]$ will at first increase more rapidly than the stoicheiometric acid concentration c, and at high concentrations will tend to a value c/n; *i.e.*, the solution will behave like a strong acid of this concentration. This corresponds closely with the behaviour observed, as shown in Fig. 1. In the more dilute solutions the acidity is low, corresponding to that of

[13] Randles and Tedder, *J.*, 1955, 1218.
[14] Broene and de Vries, *J. Amer. Chem. Soc.*, 1947, **69**, 1644.
[15] Jones and Penneman, *J. Chem. Phys.*, 1954, **22**, 781.

hydrochloric acid solutions of concentrations about 0·05c. In this range the main anionic species is HF_2^-, and we have $[H^+][HF_2^-]/[HF]_2 = \{[H^+][F^-]/[HF]\}\{[HF_2^-]/[HF][F^-]\} = 3 \times 10^{-3}$ (cf. Broene and de Vries[14]), whence $[H^+]/[HF] = (3 \times 10^{-3})^{\frac{1}{2}} = 0{\cdot}055$, independent of concentration. Between $c = 5$ and $c = 15$ the acidity increases rapidly, and above $c = 15$ it is equal to that of hydrochloric acid solutions between $c/4$ and $c/3$. In this higher concentration range the formation of $H_2F_3^-$ and $H_3F_4^-$ will lead to a rapid increase in $[H^+]$, and the behaviour of the most concentrated solutions suggests that here we have essentially a strong acid $H^+ + H_2F_3^-$ or $H^+ + H_3F_4^-$. It is not profitable to attempt a more quantitative treatment in the absence of independent information about the species present in solution and their activity coefficients.

It is noteworthy that the acidity functions of concentrated phosphoric acid solutions show a concentration dependence resembling that of hydrofluoric acid, and unlike the other weak acids.[16] It seems likely that this also is due to the formation of complex anions of strong acids, this time with the elimination of water: thus a typical ionisation scheme might be $nH_3PO_4 \rightleftharpoons H_{n+1}P_nO_{3n+1}^- + (n-1)H_2O + H^+$, with consequences similar to those for hydrofluoric acid.

Our thanks are due to the Ministry of Education for Northern Ireland for a Senior Research Award to J. C. McC.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, November 15th*, 1955.]

[16] Heilbronner and Weber, *Helv. Chim. Acta*, 1949, **32**, 1513.

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263. *The Quadrivalent Fluororhenates.*

By R. D. PEACOCK.

Complex fluorides of rhenium involving the quadrivalent ReF_6^{2-} ion have been obtained and characterised, and the acid H_2ReF_6 has been prepared in solution.

IN an earlier communication[1] the preparation of the hitherto unknown potassium fluororhenate(IV) K_2ReF_6 from the interaction of anhydrous potassium hydrogen fluoride and ammonium iodorhenate(IV) was described.

A representative selection of fluororhenates has now been prepared and some of their individual properties have been investigated. Table I shows the solubilities of these, along with those of the fluoroplatinates. Most of them are as unreactive towards water as the potassium salt, but the apparently very soluble silver and calcium salts decompose when their solutions are evaporated to dryness. From potassium fluororhenate, by using a suitable ion-exchange resin, a solution of fluororhenic acid has been prepared, but, unlike fluoroplatinic acid,[2] it cannot be isolated as a solid. Attempts to do this, even by careful evaporation at 25°, have only resulted in decomposition, with formation of the hydrated dioxide $ReO_2.nH_2O$: $H_2ReF_6 + 2H_2O \longrightarrow ReO_2 + 6HF\uparrow$. The solution, however, is stable for several weeks in the cold; it behaves as a strong acid and can be titrated in the ordinary way with alkalis.

Neither its salts nor the free acid is easily attacked by alkalis; indeed, to effect the breakdown of potassium fluororhenate quantitatively it must be fused with alkali carbonate or hydroxide. The behaviour shown by these compounds towards hydrochloric acid is again unexpected; most of the salts are unaffected even by hot, concentrated acid, and fluororhenic acid itself is attacked only after its solution has been completely evaporated to dryness, *i.e.*, under conditions when the ReF_6^{2-} ion has already been destroyed. By contrast, the neighbouring fluoro-osmates react with even dilute hydrochloric acid at 25° to give $OsCl_6^{2-}$ ion. The ReF_6^{2-} ion is attacked only slowly by alkali and hydrogen peroxide, but in acid solution is easily reduced electrolytically to the metal. This reduction to the

[1] Peacock, *Chem. and Ind.*, 1955, 1453.
[2] Clarke and Perros, *J. Amer. Chem. Soc.*, 1953, **75**, 5734.

element is not surprising, since fluorine complexes of tervalent rhenium are probably unstable, a view which receives confirmation from the fact that rhenium tri-iodide [3] breaks down to rhenium metal when fused with potassium hydrogen difluoride.

Crystallographically the fluororhenates resemble the complex fluorides of manganese and the platinum metals (Table 2). The alkali salts (except sodium) are trigonal; ammonium fluororhenate resembles most other ammonium complex metal fluorides in having a unit-cell size comparable with that of the rubidium rather than the potassium salt. Barium fluororhenate is isomorphous with the corresponding fluoro-osmate and fluoroiridate.

The available experimental data indicate that sodium fluororhenate, unlike the corresponding fluoroplatinate, could be indexed on a pseudo-cubic tetragonal cell, but more evidence is required before its structure can be definitely settled.

TABLE 1.

	Fluororhenates		Fluoroplatinates
	Colour	Solubility	Solubility [4,5]
Na_2ReF_6	White	Very soluble hot and cold	20·49
$(NH_4)_2ReF_6$	"	" "	7·32
K_2ReF_6	"	Very soluble hot; soluble cold	0·750
Rb_2ReF_6	"	Soluble hot; slightly soluble cold	0·278
Cs_2ReF_6	"	" "	0·484
$BaReF_6$	White	Soluble only when freshly pptd.	—
$[Ni(NH_3)_6]ReF_6$	Purple	Slightly soluble	—
$[Co(NH_3)_6]_2(ReF_6)_3$	Red-brown	" "	—

[a] In g./100 ml. of solution at 25°.

TABLE 2. *Crystal structures of the fluororhenates.*

		Unit-cell size (Å)	
		Fluororhenates	Fluoroplatinates [4,6]
Na_2ReF_6	Tetragonal	$a_0 = 10·02$; $c_0 = 10·14$	$a_0 = 9·41$; $c_0 = 5·16$ (trigonal)
K_2ReF_6	Trigonal	$a_0 = 5·86$; $c_0 = 4·60$	$a_0 = 5·76$; $c_0 = 4·64$
Rb_2ReF_6	"	$a_0 = 6·01$; $c_0 = 4·77$	$a_0 = 5·96$; $c_0 = 4·83$
$(NH_4)_2ReF_6$	"	$a_0 = 6·06$; $c_0 = 4·77$	—
Cs_2ReF_6	"	$a_0 = 6·32$; $c_0 = 4·99$	$a_0 = 6·22$; $c_0 = 5·01$
$BaReF_6$	Rhombohedral	$a_0 = 4·92$; $\alpha = 97·25°$	$a_0 = 4·90$; $\alpha = 97·8°$ ($BaIrF_6$)
$[Ni(NH_3)_6]ReF_6$	"	—	—
$[Co(NH_3)_6]_2(ReF_6)_3$	?Orthorhombic	—	—

Professor R. S. Nyholm has very kindly made magnetic measurements on the potassium and barium salts. For potassium fluororhenate(IV) $\mu = 3·3_2$ B.M. and for barium fluororhenate(IV) $\mu = 3·4_1$ B.M., both at 20°. The calculated spin-only value for the expected 3 unpaired electrons is $\mu = 3·88$ B.M.

EXPERIMENTAL

Reagents.—Potassium hydrogen difluoride was prepared from "AnalaR" potassium carbonate and "AnalaR" hydrofluoric acid (40%) in slight excess. The rubidium and cæsium salts were made similarly from their carbonates. Immediately before use the acid fluorides were dried at 150°. *Ammonium iodorhenate* was obtained by reduction of recrystallised ammonium per-rhenate, NH_4ReO_4, with hot "AnalaR" hydriodic acid (*d* 1·7) in the presence of recrystallised ammonium iodide. The crude product was recrystallised from hot hydriodic acid [Found: I, 77·0. $(NH_4)_2ReI_6$ requires I, 77·4%].

Potassium, Rubidium, and Cæsium Fluororhenates.—The potassium salt was prepared by slowly heating ammonium iodorhenate with potassium hydrogen difluoride to 250°. After the characteristic purple colour of the ReI_6^{2-} ion had disappeared, the temperature was gradually raised until all the ammonium salts had been driven off together with most of the hydrogen

[3] Peacock, unpublished work.
[4] Wheeler, Perros, and Naeser, *J. Amer. Chem. Soc.*, 1955, **77**, 3489.
[5] Cox, *J.*, 1954, 3251.
[6] Cox and Sharpe, *J.*, 1953, 1783.

fluoride so that a solid cake remained. After cooling, this was leached with cold water to remove most of the potassium iodide and fluoride, and the crude *potassium fluororhenate* was twice recrystallised from a little hot water (Found: Re, 49·9; F, 29·2. K_2ReF_6 requires Re, 49·2; F, 30·1%). Usually a small amount of an unidentified soluble brown material was formed during the fusion, but rapidly decomposed in the hot water to hydrated rhenium dioxide ReO_2,nH_2O, which was filtered off. *Rubidium* and *cæsium fluororhenates* were similarly prepared by using the corresponding acid fluorides (Found: Re, 39·1; F, 23·7. Rb_2ReF_6 requires Re, 39·5; F, 24·2%. Found: Re, 32·3; F, 21·0. Cs_2ReF_6 requires Re, 32·9; F, 20·1%).

Barium, Hexamminonickel, and Hexamminocobaltic Fluororhenates.—To hot aqueous potassium fluororhenate (1 g. in 50 ml.) was added excess of barium chloride solution. After filtering, an equal volume of absolute alcohol was added; *barium fluororhenate* soon separated. The solid had to be immediately recrystallised from hot water, as on ageing the precipitate soon became almost completely insoluble (Found: Ba, 31·7; Re, 42·0; F, 26·2. $BaReF_6$ requires Ba, 31·4; Re, 42·6; F, 26·0%). To a hot solution of potassium fluororhenate was added a strongly ammoniacal nickel sulphate solution. On stirring, purple *hexamminonickel fluororhenate* crystallised in needles and rhombohedral plates [Found: Ni, 12·0. $Ni(NH_3)_6ReF_6$ requires Ni, 12·7%]. *Hexamminocobaltic fluororhenate* was prepared by interaction of hot solutions of potassium fluororhenate and hexamminocobaltic chloride (Found: Co, 10·0. $[Co(NH_3)_6]_3[ReF_6]_3$ requires Co, 10·4%).

Fluororhenic Acid.—Warm, dilute, potassium fluororhenate solution was poured through a column of Zeo-Carb 225, and the colourless solution of H_2ReF_6 collected at the lower end. A N/100-solution of the acid had pH 2·6 at the glass electrode, and showed the ordinary characteristics of a strong acid when titrated with N/10-potassium hydroxide, the equivalence point being at pH 7—8.

Ammonium and Sodium Fluororhenates.—A slight excess of ammonium carbonate solution was added to fluororhenic acid solution; when the solution was evaporated nearly to dryness, crystals of *ammonium fluororhenate* appeared [Found: Re, 54·8; F, 33·6. $(NH_4)_2ReF_6$ requires Re, 55·4; F, 33·9%]. For the *sodium* compound sodium hydrogen carbonate was used. The very soluble crude salt, which sometimes appeared bluish instead of white, was recrystallised from cold water (Found: Re, 52·0; F, 32·0. Na_2ReF_6 requires Re, 53·8; F, 32·9%).

Attempted Preparation of Silver and Calcium Fluororhenates.—Solutions of these salts could be obtained by shaking freshly prepared silver or calcium carbonate in a hot fluororhenic acid solution and filtering off residual carbonate. In neither case, however, could the solid salts be obtained either by evaporating the solution to dryness or by addition of a large excess of absolute alcohol.

Attempted Direct Preparation of Ammonium Fluororhenate.—Ammonium iodorhenate was added to fused, carefully dried ammonium hydrogen difluoride, and the product dissolved in water. Owing to its high solubility, ammonium fluororhenate could not be separated from the ammonium hydrogen difluoride, but the presence of the fluororhenate ion was shown by the addition of potassium carbonate, which precipitated crystals of potassium fluororhenate.

Analysis.—The compounds were broken down by heating with fusion mixture together with a little sodium peroxide to ensure oxidation of the rhenium to the septavalent state. Rhenium was determined, after removal of interfering elements, as nitron per-rhenate; fluorine as lead chlorofluoride; barium as sulphate; cobalt as the pyridine thiocyanate complex, and nickel as dimethylglyoxime complex.

I am indebted to Messrs. Johnson Matthey and Co. Ltd. for the loan of rhenium, and to the University of London for a grant for materials.

Imperial College of Science, London, S.W.7. [*Received, November 16th*, 1955.]

264. *Ionization Constants of Heterocyclic Substances. Part II.* Hydroxy-derivatives of Nitrogenous Six-membered Ring-compounds.*

By Adrien Albert and J. N. Phillips.

Acidic and basic ionization constants are reported for 87 hydroxy(and related)-derivatives of nitrogenous six-membered heterocyclic compounds. The significance of the relative magnitudes of the values is discussed, and some useful generalizations are obtained.

The tautomeric equilibria between enol and amide in α- and γ-hydroxy-derivatives are shown greatly to favour the amide form, and in several cases the ratio has been calculated. The conclusions are supported by determination of some dipole moments.

Whereas the strengths of many heterocyclic bases and their amino-derivatives have been determined and discussed (Part I), little is known about the acidic and basic strengths of the hydroxy-derivatives. A number of such determinations are now reported (Tables 1 and 4; low values correspond to strong acids and weak bases). For monofunctional substances such as phenol and pyridine, " proton lost " corresponds to the acidic function and " proton gained " to the basic function but this simple correlation is not observed by all difunctional substances. The potentiometric method was used because of its convenience, but the more laborious spectrometric method was adopted in cases where (*a*) the solubility was too low (10^{-3}M is usually the lower limit of accuracy for potentiometric titration), (*b*) the constant was extreme (*e.g.*, potentiometry loses in accuracy when the pK is less than the logarithm of the dilution), or (*c*) the substance was too hygroscopic. Thus the results are presented at various dilutions, the effect of which on the pK of acids can be approximately calculated from the equation :

$$\mathrm{p}K_a \text{ (thermodynamic)} = \mathrm{p}K_a \text{ (as determined)} + 0{\cdot}5\sqrt{I}$$

where I is the ionic strength at half-neutralization. Thus an acid titrated at the following molarities should have the quantity in parentheses added to the pK_a values recorded here : 0·05M (0·08); 0·02M (0·05); 0·01M (0·03); 0·002M (0·02); 0·0005M (0·01). For bases, these quantities should be subtracted.

Certain of the basic constants in Table 1 turn out to be lower than had been supposed in the literature, so that ultraviolet spectra, measured at pH 2 in the belief that they were those of the cation, turn out to be those of the neutral molecule (*e.g.*, Nos. 2, 14, 16, and 27).[1]

Hydroxypyridines.—(a) *The* pK_a' *values* (*representing protons gained*). A preliminary discussion of the electronic effects of methoxyl and hydroxyl groups in a simple aromatic system is desirable to clarify the more complex situations found in the pyridine series which is, in turn, a model for the remaining series in Tables 1 and 4. The pK's of aniline and *o*-, *m*-, and *p*-methoxyaniline are [2] respectively 4·58, 4·49, 4·20, and 5·29. In *m*-methoxyaniline, only the inductive effect ($-I$) is possible, and it is base-weakening. The other isomers show the opposed influences of the $-I$ and the (base-strengthening) mesomeric effect ($+M$). The pK's of *o*-, *m*- and *p*-hydroxyaniline are [3] respectively 4·72, 4·17 and 5·50. Comparison of the *m*-derivatives shows that the inductive effect of methoxyl and hydroxyl is identical and this has been demonstrated also with acids,[4] *e.g.*, 4·09 and 4·08 respectively for *m*-methoxy- and *m*-hydroxy-benzoic acid. Inspection of the values for the *o*- and *p*-isomers reveals that the $+M$ effects of methoxyl and hydroxyl are similar, that of hydroxyl being somewhat greater.

3-Methoxypyridine (No. 8) is subject only to a ($-I$) effect and hence should be a slightly weaker base than pyridine, as is seen to be the case. Moreover, as would be predicted,

* *J.*, 1948, 2240 is regarded as Part I.

[1] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[2] Hall and Sprinkle, *ibid.*, 1932, **54**, 3469.
[3] Kuhn, *Helv. Chim. Acta*, 1928, **11**, 7.
[4] Dippy, *Chem. Rev.*, 1939, **25**, 151.

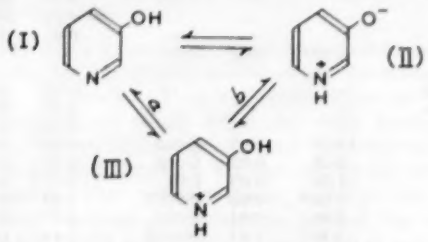
TABLE 1. *Ionization of substances having only one hetero-atom (in water at 20°).*

No.	Substance	Protons lost: pK_a	Spread [a] (±)	Concn. [a] (M)	Protons gained: pK_a'	Spread [a] (±)	Concn. [a] (M)	Analytical wavelength (μ)
1	Pyridine	—	—	—	5·23 [c]	—	—	—
2	2-Hydroxy	11·62 [a]	—	—	0·75 [f]	0·01	0·0001	296
3	3-Hydroxy	8·72 [a, b]	—	—	4·86 [b]	0·01	0·05	—
4	4-Hydroxy	11·09 [a]	—	—	3·27	0·02	0·05	—
5	2 : 4-Dihydroxy	6·50	0·01	0·02	1·37	0·03	0·05	—
		13	—	0·02				
6	2 : 4 : 6-Trihydroxy	4·6 [e]	—	0·02	—	—	—	—
		9·0	—	0·02				
		13	—	0·02				
7	2-Methoxy	—	—	—	3·28	0·06	0·01	—
8	3-Methoxy	—	—	—	4·88	0·03	0·0002	295
9	4-Methoxy	—	—	—	6·62	0·02	0·02	—
10	3-Hydroxypyridine methochloride	4·96 [d]	0·02	0·03	—	—	—	—
11	1-Methyl-2-pyridone	—	—	—	0·32	0·02	0·0001	297
12	1-Methyl-4-pyridone	—	—	—	3·33	0·02	0·02	—
13	Quinoline	—	—	—	4·93	0·02	0·0002	309
14	2-Hydroxy	11·74	0·02	0·005	−0·31 [f]	0·06	0·0005	254 (pK_a')
15	3-Hydroxy	8·06	0·03	0·005	4·30	0·05	0·005	—
16	4-Hydroxy	11·25	0·03	0·01	2·27 [m]	0·02	0·02	—
17	5-Hydroxy	8·54 [e]	0·02	0·0025	5·20	0·01	0·0025	—
18	6-Hydroxy	8·88	0·01	0·005	5·17	0·01	0·005	—
19	7-Hydroxy	8·85 [e]	0·01	0·0025	5·48	0·03	0·0025	—
20	8-Hydroxy	9·89 [a]	—	—	5·13 [a]	—	—	—
21	2 : 4-Dihydroxy	5·86	0·02	0·0001	0·76	0·05	0·00005	292 (pK_a) / 312 (pK_a')
22	2-Methoxy	—	—	—	3·17	0·03	0·001	—
23	4-Methoxy	—	—	—	6·65 [n]	—	—	—
24	1-Methyl-2-quinolone	—	—	—	−0·71	0·1	0·0002	254
25	1-Methyl-4-quinolone	—	—	—	2·46 [n]	—	—	—
26	*iso*Quinoline	—	—	—	5·46	0·02	0·002	332
27	1-Hydroxy	— [f]	—	—	−1·2	0·2	0·0002	272
28	1-Methoxy	—	—	—	3·05	0·02	0·0001	331
29	2-Methyl*iso*quinolone	—	—	—	−1·8	0·1	0·0001	276
30	Acridine	—	—	—	5·62	0·02	0·0002	403
31	3-Hydroxy	8·81	0·03	0·00002	5·52	0·02	0·00002	432 (pK_a) / 362 (pK_a')
32	5-Hydroxy (acridone)	— [f]	—	—	−0·32	0·08	0·00002	322
33	5-Methoxy	—	—	—	7 [g]	—	—	—
34	Phenanthridine	—	—	—	4·65	0·02	0·0001	315
35	2-Hydroxy	8·79	0·04	0·00005	4·82	0·03	0·00005	383 (pK_a) / 318 (pK_a')
36	6-Hydroxy	8·43	0·03	0·00005	5·35	0·02	0·00005	331 (pK_a) / 333 (pK_a')
37	9-Hydroxy (phenanthridone)	— [f]	—	—	< −1·5	—	0·00001	336, 322, 297
38	9-Methoxy	—	—	—	2·38	0·04	0·00002	345

[a] Albert and Hampton, *J.*, 1954, 505. [b] Cf. 8·6, Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67 (no details); 8·60 ± 0·08, Metzler and Snell, *ibid.*, 1955, **77**, 2421 (spectrometric). [c] Unstable (oxidizes), hence values only approximate; no basic properties evident. [d] No other pK below 12·5. [e] 5- and 7-Hydroxyquinoline methiodide, titrated with alkali, give 6·12 and 5·56 respectively (Dr. S. F. Mason, unpublished work). [f] Very weak acid, insol. in N-sodium or -potassium hydroxide. [g] Hydrolyses too fast for an exact determination. [h] These results are given only for new determinations. [i] From Part I; cf. 5·16 (25°), thermodynamic, Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26. [j] Cf. 1·28, Swain and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2538 (from one measurement only); 1·23, Stiller, Kerestezy, and Stevens, *ibid.*, 1939, **61**, 1237; both authors used potentiometry which is unsuitable for so low a value. The value 5·03 (25°) for "α-hydroxy-β-ethylpyridine" (Hall and Sprinkle, *ibid.*, 1932, **54**, 3469) must refer to 2-ethyl-3-hydroxypyridine. [k] Cf. 4·76, Stiller *et al.* (ref. *j*); 5·10 ± 0·16, Metzler and Snell (ref. *b*). [l] Cf. 5·5, Veley, *J.*, 1908, **93**, 2138 (methyl-orange method). [m] Cf. 2·34 (and 11·06), Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923 (potentiometric, 30°). [n] From Tucker and Irvin (ref. *m*), corrected from 30° to 20°. [o] An entry in this column signifies that the determination was spectrometric (otherwise potentiometric).

3-hydroxypyridine (No. 3) gives the same pK on adding acid as does 3-methoxypyridine but here there is a complicating factor. The addition of alkali to 3-hydroxypyridine methochloride (No. 10) gives a pK of 4·96, similar to that obtained by adding acid to No. 3,

although it arises by the loss of a proton from the 3-hydroxy-group of No. 10. Thus the pK of 4·86 in 3-hydroxypyridine must correspond to two distinct processes (*a*) and (*b*), and this substance must be present in aqueous solution both as the neutral molecule (I) and the dipolar ion (II). Metzler and Snell [5] recently reached this conclusion from spectrometric evidence: 3-hydroxypyridine has two peaks above 250 mμ; that at 313 μ agrees with the sole peak of the methochloride, the other (at 277 μ) agrees with that of 3-methoxypyridine. This enabled them to estimate that approximately equal amounts of the forms (I) and (II) are present in neutral aqueous solution. The addition of a little alcohol causes the peak of the dipolar form (313 μ) to vanish.[5] Also the dipole moment of 3-hydroxypyridine in benzene and dioxan (Table 3) shows that the neutral molecule is the principal species in such solvents, because the dipole moment of (II) would be of the order of 16 D.



The high proportion of the dipolar ion in aqueous solutions of 3-hydroxypyridine is due to the mutual inductive effect of the two groups: the cation strengthens the acid group, and the anion strengthens the basic group. This effect should therefore fall off with distance and be quite small in such substances as 6-hydroxyquinoline (No. 18), where 5·17 may be taken as the basic, and 8·88 as the acidic value. But in 3-hydroxypyridine, 4·86 is compounded of the basic constant of (I) (*i.e.*, addition of proton to nitrogen) and the acidic constant of (III) [*i.e.*, loss of proton to give the oxygen-anion (II)]. In the present case, where roughly equal amounts of (I) and (II) are present, these constants are equal, and may be calculated [5] to be 5·2 (a ten-fold decrease in the amount of dipolar ion would make the observed constant and the true basic constant, as defined here, practically identical). The observed pK_a of 8·72 for 3-hydroxypyridine is similarly compounded of two constants, each of which is 8·42. Thus 3-hydroxypyridine is intermediate between nicotinic acid * (which is about 95% dipolar in neutral solution [6]) and *p*-aminobenzoic acid (where the groups hardly interact). An analogy from aliphatic chemistry is provided by cysteine where two constants are shared almost equally by the mercapto- and the ammonium groups.[7]

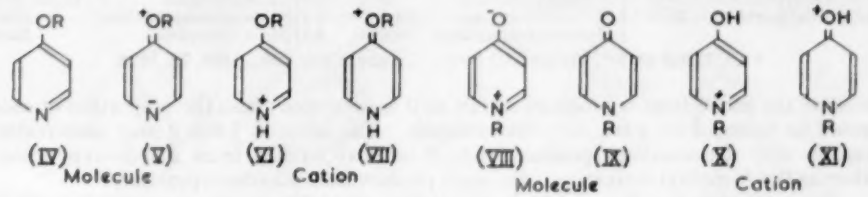
The 2- and 4-derivatives of pyridine, because of tautomeric possibilities, present a more complex picture which was clarified by preliminary study of the *O*- and the *N*-methyl derivatives. In 2- and 4-methoxypyridine (Nos. 7 and 9), the inductive effect of the methoxy-group is modified by a mesomeric effect. In the neutral molecule, resonance between forms such as (IV) and (V; R = Me) should be slight because *both* the oxygen and the nitrogen in the latter bear charges in opposition to the natural order of electronegativities. On the other hand, the cations (VI) and (VII) are capable of a moderate degree of resonance, a base-strengthening effect which overcomes the base-weakening inductive effect more successfully in the 4- than in the 2-derivative, as would be expected.

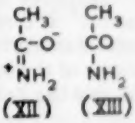
The *N*-methyl derivatives of 2- and 4-hydroxypyridine (Nos. 11 and 12) have a very different distribution of electrons from their *O*-methyl isomers. Admittedly the resonance of the cations is similar for *O*- and *N*-derivatives [*i.e.*, the pair (X) ◄► (XI), differs from

* The values [6] are 2·09 (carboxyl) and 4·77 (nitrogen), evidence of less interaction than in 3-hydroxypyridine because of a smaller inductive effect. Here, as in other comparisons in this paper, the simplifying and reasonable assumption is made that the degree of hydration is of the same order of magnitude.

[5] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.
[6] Jaffé, *ibid.*, p. 4445.
[7] Grafius and Neilands, *ibid.*, p. 3389.

the pair (VI) ◄► (VII) only by substitution of methyl for hydrogen]. On the other hand, the resonance of the neutral form, *i.e.*, between (VIII) and (IX), must be much greater in the *N*-methyl derivatives because the oxygen and the nitrogen atoms bear charges in accordance with their relative positions in the electronegativity scale [contrast (VIII) with (V)].* Dipole-moment measurements confirm that the neutral molecules of the *N*-methyl isomers are more highly polar than those of the *O*-methyl isomers (Table 3).





Accordingly it is not surprising to find that the *N*-methyl derivatives are much weaker bases than their *O*-methyl isomers. Of these *N*-methyl derivatives, the α-isomer (No. 11) is weaker than the γ-isomer (No. 12) because the close approach of the groups in No. 11 increases the ion–dipole interaction whereby the positively charged nitrogen atom hinders approach of a proton to the oxygen atom. It is not a steric effect because 2-*tert.*-butylpyridine is not appreciably weaker than 2-methylpyridine.[8]

2- and 4-Hydroxypyridine can now be discussed. Table 1 shows that their affinity for protons is similar to that of their *N*-methyl (and far below that of their *O*-methyl) derivatives. Thus the enolic tautomer, such as (IV; R = H), must play an exceedingly small part in the equilibrium state of these substances, whereas the strong resonance between the dipolar ion and the amide (VIII and IX; R = H) predominates. (The argument has been simplified by omitting minor contributions to resonance hybrids, especially forms with a charge upon carbon, which, although significant for pyridine itself, should become less so when two polarizable atoms are present.) These two hydroxypyridines may be compared with acetamide where the low [9] pK_a (−0·5) is a consequence of resonance [10] (21 kcal./mole) between (XII) and (XIII). In effect, α-hydroxypyridine is a cyclic amide, and 4-hydroxypyridine is a vinylogous [11] amide.

Results in Table 1 permit calculation [12] of the ratio of amide to enol tautomers [*i.e.*, the ratio of the hybrid (VIII) ◄► (IX) to (IV) (R = H in all cases)] in the hydroxy-derivatives at equilibrium in aqueous solution, by using the equation

$$\log R = \mathrm{p}K_{\mathrm{OMe}} - \mathrm{p}K_{\mathrm{OH}}$$

where R is the ratio of amide to enol tautomers, and pK_{OMe} and pK_{OH} are the observed values for the addition of a proton to corresponding methoxy- and hydroxy-compounds. This method assumes that the intrinsic basic constant for, say, (IV; R = H) would differ little from that of (IV; R = Me) (that this is a reasonable assumption may be gauged by reference to the values of the methoxy- and hydroxy-anilines, above). The results are

* The relation between this resonance hybrid and the small amount of enol (*e.g.*, IV, where R = H) with which it is in equilibrium is discussed below. The example of 3-hydroxypyridine (above) showed that the tendency to form dipolar ions, *e.g.*, (II), is strong even when these are not stabilized by resonance, as (VIII) is.

[8] Brown and Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.
[9] Hall, *ibid.*, 1930, **52**, 5115.
[10] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1942, p. 138.
[11] Fuson, *Chem. Revs.*, 1935, **16**, 1.
[12] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923; cf. Edsall and Blanchard, *ibid.*, 1933, **55**, 2337.

given in Table 2 and show a wide range of values. Although a vanishingly small amount of the enolic form is present in 5-hydroxyacridine, chlorination (to 5-chloroacridine) by phosphorus oxychloride occurs no less readily than with 2-hydroxypyridine, doubtless

TABLE 2. *Approximate ratio of amide to enol tautomers* [i.e., *of the hybrid* (VIII) ◄► (IX) *to* (IV) (R = H *in all cases*)] *in neutral aqueous solution at* 20°.

2-Hydroxypyridine ...	340	2-Hydroxyquinoline ...	3000	5-Hydroxyacridine	10,000,000
4-Hydroxypyridine ...	2200	4-Hydroxyquinoline ...	24,000 [a]	9-Hydroxyphenanthridine	8000
		1-Hydroxyisoquinoline	18,000	4-Hydroxycinnoline	3600

[a] Cf. 12,900 at 30°, Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.

because the enolic form is produced as fast as it is consumed; also the proportion of enol would be favoured by a low dielectric constant. The ratios in Table 2 may conceivably explain why diazomethane produces only 2-methoxypyridine from 2-hydroxypyridine, whereas the *N*-methyl derivative is the main product from 4-hydroxypyridine.[13]

The conclusion that 2- and 4-hydroxypyridine are highly dipolar resonance hybrids is supported by dipole-moment measurements. It is clear from Table 3 that these substances are considerably more polar than their *O*-methyl derivatives. Unfortunately, no fine analysis of the results is practicable because of the sensitivity of moments to slight changes in structure, such as valency angles and (for the 2-derivatives) freedom of rotation.

TABLE 3. *Dipole moments* (μ; *in* D) *of pyridine derivatives in benzene at* 25°.

Substance	2-	3-	4-
Hydroxypyridine	1·95 [a]	2·00 [b]	(5·3) [d]
O-Methyl derivative	1·15	2·75	3·00
N-Methyl derivative	4·15	— [c]	6·9

[a] 2·95 in dioxan. [b] 2·95 in dioxan. [c] Too insoluble for determination. [d] Too insoluble in benzene for direct determination, the figure being calculated from the value in dioxan (6·30; cf. 6·0, Curran and Leis, *J. Amer. Chem. Soc.*, 1952, **74**, 4584).

(b) *The* pK_a *values* (*representing protons lost*). Table 1 shows that 2- and 4-hydroxypyridine are much weaker acids than the 3-isomer [this is a simpler approach than that of concentrating attention solely on the dipolar ion (VIII; R = H) by referring to, say, 2-hydroxypyridine as an acid of pK 0·75, comparable in strength with mineral acids]. The weakness of these acids is understandable by analogy with acetamide [14] (pK = 15·1) which has a strong resonance between the neutral forms (XII) and (XIII) resulting in great acid-weakening. Thus 4-hydroxypyridine is weakened as an acid by the high resonance stabilization of the neutral forms, (VIII and IX; R = H), which was discussed above.

Because very little enol (IV; R = H) is present in the neutral molecule, these constants accurately represent the ionization of the hybrid (VIII) ◄► (IX) (R = H). However, the following equation enables a value (pK_E) to be calculated [5] for the ionization of an enol:

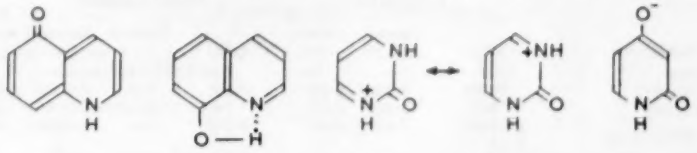
$$pK_E = pK_a - \log (R + 1)$$

(where pK_a is the value as determined and R is the ratio of tautomers from Table 2). This gives pK_E values for 2- and 4-hydroxypyridine of 9·09 and 7·74 respectively, to be compared with 8·72 for the 3-isomer (or, more correctly, 8·42, corrected for 50% dipolar ion by the above equation). These figures may be compared with the values for phenol [15] and its *o*-, *m*- and *p*-nitro-derivatives,[16] respectively 9·98, 7·25, 8·28, and 7·21; all nitrophenols show the inductive effect (−*I*) of the nitro-group, the *o*- and *p*-isomers also show a mesomeric effect (−*M*), both of which are acid-strengthening, and the *o*-isomer also has an *ortho*-effect which is acid-weakening. Qualitatively the same influences seem to be present in the hydroxypyridine enols, and, on the evidence of 3-hydroxypyridine, the

[13] Mosher in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, p. 534; Meyer, *Monatsh.*, 1905, **26**, 1311.
[14] Branch and Clayton, *J. Amer. Chem. Soc.*, 1928, **50**, 1680.
[15] Bordwell and Cooper, *ibid.*, 1952, **74**, 1058.
[16] Wheland, "The Theory of Resonance," Wiley, New York, 1944, p. 172; Martin and Butler, *J.*, 1939, 1366.

inductive effect of an uncharged ring-nitrogen atom is quantitatively similar to that of a nitro-group.

General Discussion.—It is now possible to apply these generalizations to the remaining substances in Tables 1 and 4. The pK_a and pK_a' values of 2-, 3-, and 4-hydroxyquinoline (Nos. 14—16) and their *O*- and *N*-methyl derivatives resemble those of the corresponding pyridines and are explicable similarly. 5-, 6-, and 7-Hydroxyquinoline appear to be normal phenols and it is interesting that the values for 5-hydroxyquinoline (No. 19) do not suggest any great content of the transannular tautomer (XIV). 8-Hydroxyquinoline is a



(XIV) (XV) (XVI) (XVII) (XVIII)

weaker acid than these, the bonding of the ionizable hydrogen atom between oxygen and hydrogen, as (XV), making it less mobile.

The interpretation of α- and γ-hydroxypyridine, existing in aqueous solution mainly as amides rather than as enols, can be applied not only to the quinolines (see above) but also (among the one-nitrogen systems) to the *iso*quinoline, phenanthridine, and acridine series (see Table 1). Table 4 shows that it can also be applied to the pyridazine, pyrimidine, and pyrazine series (among two-nitrogen monocyclic systems), to the cinnoline, phthalazine, quinazoline, quinoxaline, and naphthyridine series (among two-nitrogen bicyclic systems), and also in more complex series. 2-Hydroxypyrimidine (No. 47) is an unusual example of an α-hydroxy-group's not depressing the basic strength of the parent substance, because the symmetrical structure of the cation of the amide form makes possible an unusual base-strengthening resonance (XVI) ◄► (XVII).

That α- and γ-hydroxy-compounds exist mainly in the amide form ***in the solid state*** has been established by *X*-ray crystallography for 2-hydroxypyridine,[17] 2 : 4-dihydroxypyrimidine [18] and 2 : 4 : 6-trihydroxy-1 : 3 : 5-triazine,[19] and by infrared spectrometry for 2- and 4-hydroxypyrimidine;[20] ***in aqueous solution*** by ultraviolet spectrometric comparison with *O*- and *N*-methyl derivatives for 2- and 4-hydroxypyridine,[21] 2-hydroxyquinoline,[22] 5-hydroxyacridine,[23] 2- and 4-hydroxypyrimidine [20] and their *C*-alkyl-derivatives,[24] 2 : 4-dihydroxypyrimidine,[21] 4-hydroxyquinazoline,[25] and 4-hydroxycinnoline [25] (also, but not adequately, for 4-hydroxyquinoline, 1-hydroxy*iso*quinoline, 3-hydroxypyridazine, 3-hydroxycinnoline, and 2-hydroxypyrazine [26]). None of these methods can detect even 1% of a minor constituent and hence cannot furnish the information on ratios presented above; however, their confirmation that the amide is the major product is welcome.

It is, in general, not desirable to extend to rings containing two or more nitrogen atoms the calculations of amide : enol ratios used for the one-nitrogen rings, for it cannot be assumed with any certainty that the same nitrogen is protonated in the pair of compounds being contrasted. However in such cases as 4-hydroxycinnoline, where only one of the nitrogen atoms can take part in the tautomerism, the calculation can be used with some confidence.

The polyhydroxy-pyridines and -quinolines (Nos. 5, 6, 21) lose the first proton at a

[17] Penfold, *Acta Cryst.*, 1953, **6**, 591.
[18] Parry, *ibid.*, 1954, **7**, 313.
[19] Newman and Badger, *J. Amer. Chem. Soc.*, 1952, **74**, 3545.
[20] Brown, Hoerger, and Mason, *J.*, 1955, 211; Brown and Short, *J.*, 1953, 331.
[21] Specker and Gawrosch, *Ber.*, 1942, **75**, 1338.
[22] Ley and Specker, *ibid.*, 1939, **72**, 192; Ault, Hirst, and Morton, *J.*, 1935, 653.
[23] Acheson, Burstall, Jefford, and Sansom, *J.*, 1954, 3742.
[24] Marshall and Walker, *J.*, 1951, 1004.
[25] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[26] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; Alford and Schofield, *J.*, 1953, 1811; Dutcher, *J. Biol. Chem.*, 1947, **171**, 321; Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1954, **37**, 1298.

much lower pH than their monohydroxy-analogues. This seems to be due to action of one of the hydroxy-groups as a normal aromatic phenol whilst the other is engaged in the amide resonance. An acid-strengthening resonance, involving (XVIII) and a similar anion with the charge on the other oxygen atom, is also possible but it makes only a minor contribution here because symmetrically equivalent structures are not involved. There is no acid-strengthening in the monoanion of 2 : 4-dihydroxypyrimidine where both hydroxyl groups

TABLE 4. *Ionization of substances having two hetero-atoms, in water at 20°.*

		Protons lost			Protons gained			
No.	Substance	pK_a	Spread (±)	Concn. (M)	pK_a'	Spread (±)	Concn. (M)	Analytical wavelength (μ)
39	Pyridazine	—	—	—	2·33[g]	—	—	—
40	3-Hydroxy	10·46	0·03	0·02	−1·8	0·3	0·0002	285 (pK_a')
41	4-Hydroxy	8·68	0·01	0·02	1·07	0·03	0·00005	262 (pK_a')
42	3 : 6-Dihydroxy	5·67 13	0·01	0·02	−2·2	0·4	0·0002	300 (pK_a')
43	3-Methoxy	—	—	—	2·52	0·01	0·02	—
44	4-Methoxy	—	—	—	3·70	0·02	0·02	—
45	3 : 6-Dimethoxy	—	—	—	1·61[f]	0·01	0·02	—
46	Pyrimidine	—	—	—	1·30[g]	—	—	—
47	2-Hydroxy	9·17[a]	—	—	2·24[a]	—	—	—
48	4-Hydroxy	8·59[b]	—	—	1·85[b]	—	—	—
49	2 : 4-Dihydroxy (Uracil)	9·38[a] 12	0·06	0·01	—	—	—	—
50	4 : 5-Dihydroxy	7·48 11·61	0·01 0·07	0·02 0·02	1·99[f]	0·03	0·05	—
51	4 : 6-Dihydroxy	5·4[d]	—	0·02	—	—	—	—
52	2 : 4 : 5-Trihydroxy (*iso*Barbituric acid)	8·11[a] 11·48[f]	0·02 0·03	0·01 0·01	—	—	—	—
53	2 : 4 : 6-Trihydroxy (Barbituric acid)	3·9[g] 12·5	—	—	—	—	—	—
54	2 : 4 : 5 : 6-Tetrahydroxy (Dialuric acid)	2·83[h] 11	—	—	—	—	—	—
55	2-Methoxy	—	—	—	<1	—	0·02	—
56	4-Methoxy	—	—	—	2·5[g]	—	—	—
57	4-Hydroxy-5-methoxy	8·60	0·02	0·02	1·75[f]	0·04	0·02	—
58	1-Methyl-2-pyrimidone	—	—	—	2·50	0·04	0·03	—
59	1-Methyl-4-pyrimidone	—	—	—	1·8[g]	—	0·05	—
60	3-Methyl-4-pyrimidone	—	—	—	1·84	0·03	0·03	—
61	Pyrazine	—	—	—	0·6[g]	—	—	—
62	2-Hydroxy	8·23[f]	—	—	−0·1[g]	0·08	0·0005	360, 275
63	2-Methoxy	—	—	—	0·75[f]	0·04	0·05	—
64	1-Methyl-2-pyrazone	—	—	—	−0·04	0·06	0·0001	350
65	Cinnoline	—	—	—	2·29[h]	—	—	—
66	3-Hydroxy	8·64	—	—	0·21	0·04	0·0002	395
67	4-Hydroxy	9·27	0·03	0·01	−0·35	0·05	0·00005	337
68	5-Hydroxy	7·40[h]	—	—	1·92[h]	—	—	—
69	6-Hydroxy	7·52[h]	—	—	3·65[h]	—	—	—
70	7-Hydroxy	7·56[h]	—	—	3·31[h]	—	—	—
71	8-Hydroxy	8·20[f]	—	—	2·74	—	—	—
72	4-Methoxy	—	—	—	3·21[f]	—	—	—
73	Phthalazine	—	—	—	3·47[g]	—	—	—
74	1-Hydroxy	11·99[f]	0·02	0·01	−2	—	0·0002	308
75	Quinazoline	—	—	—	3·51[g]	—	—	—
76	2-Hydroxy	10·69	0·03	0·0002	1·30	0·02	0·0002	360 (pK_a) 390 (pK_a')
77	4-Hydroxy	9·81	0·02	0·033	2·12	0·05	0·033	—
78	6-Hydroxy	8·19	0·01	0·005	3·12	0·03	0·005	—
79	8-Hydroxy	8·65[f]	—	—	3·41[f]	—	—	—
80	3-methiodide	7·26[f]	—	—	—	—	—	—
81	2 : 4-Dihydroxy	9·78	0·03	0·0005	2·5[a]	—	0·0005	—
82	2-Methoxy	—	—	—	1·31[f]	0·08	0·02	—
83	4-Methoxy	—	—	—	3·13[f]	—	—	—
84	Quinoxaline	—	—	—	0·56[g]	0·04	0·0005	362
85	2-Hydroxy	9·08[f]	—	—	1·37	0·07	0·003	400 (pK_a')
86	5-Hydroxy	8·65[f]	—	—	0·9[f]	—	—	—
87	1-methiodide	5·74[f]	—	—	—	—	—	—
88	6-Hydroxy	7·92	0·02	0·002	1·40	0·02	0·0002	400 (pK_a')
89	2 : 3-Dihydroxy	9·52	0·04	0·001	—	—	—	—
90	1 : 5-Naphthyridine	—	—	—	2·91	0·03	0·05	—
91	4-Hydroxy-	10·01[f]	—	—	2·85[f]	—	—	—

TABLE 4. (*Continued.*)

No.	Substance	Protons lost: pK_a	Spread (±)	Concn. (M)	Protons gained: pK_a'	Spread (±)	Concn. (M)	Analytical wavelength (μ)
92	Phenazine	—	—	—	1·23 [g]	—	—	—
93	1-Hydroxy	8·5 [m]	—	—	1·44 [m]	—	—	—
94	2-Hydroxy	7·5 [n]	—	—	2·6 [n]	—	—	—
95	5-Methyl-1-phenazone	—	—	—	4·9 [w]	—	—	—
96	10-Methyl-2-phenazone	—	—	—	3·0 [n]	—	—	—
	Substances with three hetero-atoms							
97	1 : 3 : 5-Triazine	— [o]	—	—	—	—	—	—
98	2 : 4-Dihydroxy	6·5 [p]	—	0·02	—	—	—	—
99	1 : 4 : 5-Triazanaphthalene	—	—	—	1·20 [f]	0·03	0·05	—
100	8-Hydroxy	8·76 [t]	—	—	0·60 [t]	0·03	0·0002	280
101	1 : 4 : 6-Triazanaphthalene	—	—	—	2·5 [t]	—	0·05	—
102	5-Hydroxy	11·05 [t]	—	—	−0·78 [t]	0·03	0·0002	400

[a] Brown, *Nature*, 1950, **165**, 1010. [b] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [c] Cf. 9·3 (and >13), Shugar and Fox, *Biochim. Biophys. Acta*, 1952, **9**, 199 (spectrometric); 9·45, Levene, Bass, and Simms, *J. Biol. Chem.*, 1926, **70**, 229 (potentiometric, 25°). [d] Unstable to alkali (slow decomposition). [e] Cf. 8·4 (approx.), Wood, *J.*, 1906, **89**, 1831 (hydrolysis of ethyl acetate). [f] Thermodynamic value obtained by correction for the mean ionic activity with Davies's coefficient (*J.*, 1938, 2093); this reduces the large spread encountered in potentiometry when pK's lie outside the range 3—11. [g] From Fox and Shugar, *Bull. Soc. chim. belges*, 1952, **61**, 44 (spectrometric). [h] From Richardson and Cannan, *Biochem. J.*, 1929, **23**, 68 (potentiometric, H_2 electrode, 30°). [i] Albert, Brown, and Cheeseman, *J.*, 1952, 1620. [j] From Alford and Schofield, *J.*, 1953, 1811 (potentiometry). [k] Unpublished values determined by Dr. K. Schofield (Exeter) on material synthesized in his laboratory, and quoted here by kind permission. [l] Albert and Hampton, *J.*, 1954, 505 (see this also for 8-hydroxy-1 : 6- and -1 : 7-naphthyridine). [m] From Muller, *J. Biol. Chem.*, 1942, **145**, 425. [n] From Preisler and Hempelmann, *J. Amer. Chem. Soc.*, 1937, **59**, 141. [o] This very weak base was almost instantly destroyed by water and no value could be obtained. [p] Slowly hydrolysed by alkali during titration. [q] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [r] Brown and Short, *J.*, 1953, 311. [s] Unstable (hydrolysis). [t] Kindly determined by Dr. S. F. Mason. [u] Back-titration. [v] Albert, Brown, and Wood (*J.*, 1954, 3832) obtained 0·72 ± 0·1 (potentiometrically at 0·1M, a method now considered not sufficiently accurate for so low a value). [w] From Michaelis, Hill, and Schubert, *Biochem. Z.*, 1932, **255**, 70.

are engaged in amide resonances (cf. Nos. 48 and 49; also Nos. 77 and 81). 4 : 5- and 4 : 6-Dihydroxypyrimidine (Nos. 50 and 51) are stronger acids because only one hydroxyl group can tautomerize to an amide (restriction by valency). Of these, the 4 : 6-isomer is yet stronger because the anion can form a resonance hybrid from symmetrical structures. Because barbituric acid (No. 53) and its *NN'*-dimethyl derivative have similar spectra and acidities, Fox and Shugar [27] concluded that the same group is ionizing in both at about pH 4, but they are not necessarily correct in attributing this to the methylene group rather than a truly phenolic 6-hydroxy-group. True, inserting two ethyl groups in the 5-position raises the pK to 7·8, but such acid-weakening would be expected in the non-aromatic structure thus produced.

Finally, the effect of a second nitrogen atom on an α- or γ-hydroxyl substituent is to increase the acidic strength greatly. The general inductive effect of the additional nitrogen atom disturbs the acid-weakening (amide) resonance by drawing upon electrons necessary for its operation (compare Nos. 41 and 48 with No. 4, and Nos. 47 and 62 with No. 2). Three ring-nitrogen atoms intensify this effect (No. 98).

In addition to the constants given in Tables 1 and 4, those of a number of hydroxypteridines [28] and hydroxypurines [29] are available.

EXPERIMENTAL

Potentiometric Titrations.—0·0005 Mole of the dried specimen was dissolved in air-free water and titrated under nitrogen, a Cambridge pH set being used with glass and calomel electrodes (standardized to pH 4·00 with 0·05M-potassium hydrogen phthalate and 9·20 with 0·05M-borax at 20°). Agreement on restandardization of this instrument after a titration was ±0·01 unit. 0·9 Equivalent of hydrochloric acid, or of carbon dioxide-free potassium hydroxide, was added

[27] Fox and Shugar, *Bull. Soc. chim. belges*, 1952, **61**, 44.
[28] Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 1620. Albert and Brown, *J.*, 1953, 74.
[29] Albert and Brown, *J.*, 1954, 2060.

in nine equal portions. The nine pK values for each pH reading were calculated (when acid was the titrant) from the formula:

$$pK_a = pH - \log ([B] + [H^+]/[BH^+] - [H^+])$$

where $[BH^+]$ and $[B]$ are the concentration of the molecule, protonated and non-protonated respectively, if hydrolysis corrections (taken care of by the rest of the formula) are neglected; and (when alkali was the titrant) from:

$$pK_a = pH + \log ([AH] - [H^+]/[A^-] + [H^+])$$

The nine pK values were converted into antilogarithms before averaging. The small spreads encountered gave additional confirmation of the purity of the substance. Solutions of the substance were made as concentrated (but not above 0·05M) as solubility permitted to keep the hydrolysis corrections low. The strength of the titrant was 0·1N (added from a burette), or N (from a micrometer syringe) for the more concentrated solutions.

Spectrometric Determinations of pK.—Solutions were made in a series of buffers, standardized with a glass electrode. This series decreased in pH down to values where the change in spectrum, corresponding to the step of ionization under study, ceased; and similarly it increased towards the alkaline direction. Buffers (0·01M) of low ultraviolet absorption (glycine, borate, phosphate, acetate, and formate) were used, and for low values the hydrogen-ion exponent solutions (sulphuric acid) of Hammett and Paul.[30] Measurements were made in the Hilger "Uvispek" ultraviolet spectrophotometer (1 cm. cells). Buffer solutions of the same strength were used as controls. At wavelengths selected because of marked differences found between the extinction coefficients of the neutral molecule (ε_M) and that of the protonated form (ε_{MH^+}), the extinction coefficients of the sum of the two species (ε) were measured at such pH values as were found, during the course of the determinations, to correspond to the range from 15 to 85% protonation in 8 equal steps. The pK's were determined from the following formula:

$$pK_a = pH - \log [(\varepsilon_{MH^+} - \varepsilon)/(\varepsilon - \varepsilon_M)]$$

converted into antilogarithms, and averaged. No hydrolysis correction is required in this method, but the usual activity corrections apply.[31]

Dipole Moments.—A conventional apparatus of improved design [32] was used. The benzene was dried (Na) and freshly distilled, the dioxan was first refluxed with sodium for 8 hr. The *O*- and *N*-methyl derivatives were dried (NaOH) and refractionated immediately before use; 2-hydroxypyridine was dried (P_2O_5) at 20°/20 mm. for 24 hr., 3-hydroxypyridine for 1 hr. in air at 110°, 4-hydroxypyridine first as for the 2-isomer, then at 100°/0·01 mm. for 1 hr. All substances are hygroscopic and were handled expeditiously. The moments were calculated from the approximate relation proposed by Smith.[33] The reported values are the mean of 5—7 determinations at different concentrations. The values agreed within ±0·05 D.

Preparations (Analyses by Mr. P. R. W. Baker, Beckenham).—Many of the substances are well known and were purchased or made by well-established methods. They were purified to the constants given in the literature and in addition examined for extraneous material by paper-chromatography in aqueous ammonium chloride (3%) and in butanol–acetic acid. α- and γ-Methoxy-compounds were made only by the action of sodium methoxide on the corresponding chloro-compounds, and not by direct methylation, so as to avoid contamination with the *N*-methyl isomers. They were fractionated under reduced pressure and measured immediately after preparation, because of their tendency to isomerize. After measurement, it was confirmed spectrometrically that only 5-methoxyacridine had undergone any acid-catalysed hydrolysis.

3-Methoxypyridine was made from 3-hydroxypyridine (m. p. 126°) and diazomethane by a method used for 3-methoxy-5-methylpyridine.[34]

3-Hydroxypyridine methochloride. Methyl iodide (0·62 ml., 1 equiv.) was refluxed for 1 hr. with 3-hydroxypyridine (0·95 g.) in benzene (60 ml.). The crystals were washed with boiling benzene, dissolved in water (5 ml.), and shaken with silver oxide (1, then 0·1, equiv.). The filtrate (pH 8·5) was extracted with ether (50 + 50 ml., discarded) to remove any 3-methoxypyridine, acidified to pH 2 with hydrochloric acid, and allowed to crystallize in a desiccator

[30] Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 827; Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 268.
[31] Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26.
[32] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.
[33] Smith, *ibid.*, 1950, **46**, 394 (equation 9).
[34] Marion and Cockburn, *J. Amer. Chem. Soc.*, 1949, **71**, 3402.

(Found: C, 49·9; H, 5·55; N, 9·65; Cl, 24·15. Calc. for C_9H_8ONCl: C, 49·5; H, 5·55; N, 9·6; Cl, 24·35%).

3-*Hydroxyquinoline* (with Dr. J. H. Lister). The published method gives poor yields because of self-coupling.[35] The solid diazonium chloride [36] from 3-aminoquinoline (3·7 g.) was added slowly to boiling water (80 ml.). After 30 minutes' further boiling, the solution was treated with charcoal, then cooled, and an excess of sodium hydrogen carbonate was added. The base was filtered off and recrystallized from dilute ethanol (yield, 48%; m. p. 198°).

1-*Hydroxyisoquinoline*. *iso*Quinoline (6·5 g.), acetic acid (15 ml.), and 30% hydrogen peroxide (4·5 ml.) were heated for 3 hr. at 70°. Further hydrogen peroxide (4·5 ml.) was added and heating continued for 3 hr. More hydrogen peroxide (4·5 ml.) was added again and the mixture evaporated in a vacuum at 70°. 2N-Sodium carbonate was added to the residue (until alkaline), which was shaken with chloroform (4 × 50 ml.). The chloroform layer was dried (K_2CO_3) and taken to dryness. The residue was ground under ether, filtered, and dried, giving 5 g. of *iso*quinoline *N*-oxide dihydrate, m. p. 98° (cf. Ochiai *et al.*[37] who used perphthalic acid). The oxide was refluxed with 10 parts of acetic anhydride for 4 hr. The volatile material was removed *in vacuo* and the residue refluxed with 5 parts of N-sodium hydroxide for 15 min., more alkali being added until the pH ceased to fall below 10. The suspension was then brought below pH 10 with acetic acid, refrigerated, filtered, and dried, giving 3·4 g. of crude 1-hydroxy*iso*quinoline. This was recrystallized from 130 parts of boiling water, giving colourless crystals (m. p. 208°) identical with material prepared by older methods.

2-*Methyl*-1-*isoquinolone* (1 : 2-*dihydro*-2-*methyl*-1-*oxoisoquinoline*). This was prepared from *iso*quinoline methiodide by Decker's method; [38] it was distilled at 0·1 mm. and recrystallized from light petroleum; it melted at 57° (lit., 38—40°).

1-*Methoxyisoquinoline* (Dr. J. H. Lister). Fernau [39] obtained an oil, b. p. about 240°, from the silver salt of 1-hydroxy*iso*quinoline and methyl iodide and described it as 1-methoxy*iso*quinoline, the only mention in the literature. Sodium methoxide [1 equiv., from sodium (1·05 g.) in methanol (12 ml.)] and 1-chloro*iso*quinoline (6·4 g.) were refluxed for 4 hr. After chilling, sodium chloride was filtered off and washed with methanol. The filtrates were evaporated and the residue was extracted with ether. The extract was dried (KOH) and the ether recovered. The residual oil was fractionated, giving 1-methoxy*iso*quinoline (88%) as a colourless oil, b. p. 135—136°/21 mm. (Found: C, 75·2; H, 5·8; N, 9·1. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%).

Phenanthridines. The 2- and 4-hydroxy- and 9-methoxy-phenanthridines were kindly presented by Drs. C. L. Arcus and M. M. Coombs,[40] and 9-hydroxyphenanthridine by Dr. L. Walls.

Pyridazines. These were all kindly supplied by Dr. J. Druey.[41]

2 : 4 : 5-*Trihydroxypyrimidine* (Dr. D. J. Brown). This was made by simultaneous reduction and hydrolysis [42] of 5-nitrouracil, and recrystallized thrice from water (60 parts), giving white needles (Found, after drying at 120°/0·01 mm.: C, 37·15; H, 3·2; N, 21·8. Calc. for $C_4H_4O_3N_2$: C, 37·5; H, 3·15; N, 21·85%). The *O*- and *N*-methylated pyrimidines were supplied by Dr. Brown also.[39] We thank Dr. J. F. W. McOmie for a gift of 4 : 5-dihydroxy- and 4-hydroxy-5-methoxy-pyrimidine.

2-*Methoxypyrazine* (Dr. J. Lister). 2-Hydroxypyrazine [43] (5 g.) was heated at 100° with phosphorus oxychloride (30 ml.) for 40 min. The reagent was removed *in vacuo* (20 mm.) and the residue stirred into crushed ice. The recovered oxychloride was treated similarly, as some product had volatilized, and both aqueous solutions were extracted with ether (extracts dried over Na_2SO_4). The ether was recovered and the residue fractionated, giving 2-chloropyrazine, b. p. 60—61°/28 mm., in 85% yield (published yield: 58%).[43] This oil (3 g.) and methanol (3 ml.) were chilled to 0° and added to a chilled solution of sodium methoxide (1 equiv., 0·7 g. of sodium in 10 ml. of methanol). The mixture was refluxed at 120° for 2 hr. and cooled. The precipitated salt was washed with methanol, and the combined filtrates were evaporated (at

[35] Mills and Watson, *J.*, 1910, **97**, 753.
[36] Abramovitch, *J.*, 1954, 3839.
[37] Ochiai, Ishihara, and Zai-Ren, *J. Pharm. Soc. Japan*, 1944, **64**, 72; *Chem. Abs.*, 1951, **45**, 8526.
[38] Decker, *J. prakt. Chem.*, 1893, **47**, 37.
[39] Fernau, *Monatsh.*, 1893, **14**, 66.
[40] Arcus and Coombs, *J.*, 1954, 4319.
[41] Druey, Meier, and Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121; Schmidt and Druey, *ibid.*, p. 134; Eichenberger, Rometsch, and Druey, *ibid.*, p. 1298.
[42] Davidson and Baudisch, *Ber.*, 1925, **58**, 1685.
[43] Erickson and Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400.

760 mm.). The residue was dissolved in a little water and extracted with ether (extracts dried over Na_2SO_4). The ether was recovered and the *2-methoxypyrazine* (40%) distilled (b. p. 60—61°/29 mm.) (Found: C, 54·9; H, 5·4; N, 24·9. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%). 1-Methyl-2-pyrazone [44] was recrystallized from light petroleum after sublimation.

1-Hydroxyphthalazine was kindly presented by Dr. N. B. Chapman, and 4-methoxycinnoline by the late Dr. J. Simpson.

2-Hydroxyquinazoline. This substance is poorly described in the literature. Prof. B. E. Christensen kindly supplied a specimen prepared from 2-aminobenzaldehyde and urea.[45] This was purified through the hydrochloride. Part of it was converted through 2-chloro- into 2-methoxy-quinazoline,[45] and the latter was refluxed with 0·5N-alcoholic sodium hydroxide for 4 hr. The solution was neutralized, evaporated, and extracted with ether, and then with cold water. The residue, a poorly soluble white powder, was chromatographically identical with the starting material. When boiled with 200 parts of water, both specimens dissolved in 2 hr. and deposited nothing on concentration to 20 parts and chilling. This behaviour is suggestive of ring-opening because evaporation in the presence of a trace of acid regenerated the original poorly soluble material. For determination of pK, it was dissolved in acid, and the solution diluted with the requisite buffers.

1 : 5-Naphthyridine [47] and 1 : 4 : 5-triazanaphthalene [48] and the 1 : 4 : 6-isomer [49] were purified by sublimation (all prepared by Mr. C. Pedersen).

1 : 3 : 5-Triazine [50] was kindly presented by Dr. C. Grundmann. 2 : 4-Dihydroxytriazine was prepared by the oxidation of uric acid.[51]

We thank Dr. J. W. Smith for advice on the determination of dipole moments; also our colleagues: Dr. S. F. Mason for helpful discussions, Dr. D. J. Brown, Dr. J. H. Lister, and Mr. C. Pedersen for carrying out the preparations to which their names are attached; also Mr. K. Tratt for general assistance. All pK values not otherwise indicated were determined by the Department's head technician, Mr. E. P. Serjeant, to whom our best thanks are offered.

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[44] Dutcher, *J. Biol. Chem.*, 1947, **171**, 321.
[45] Gabriel and Stelzner, *Ber.*, 1896, **29**, 1300.
[46] Bogert and May, *J. Amer. Chem. Soc.*, 1909, **31**, 512.
[47] Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081.
[48] Leese and Rydon, *J.*, 1955, 303.
[49] Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690.
[50] Grundmann and Kreutzberger, *J. Amer. Chem. Soc.*, 1954, **76**, 5646.
[51] Brandenberger and Brandenberger, *Helv. Chim. Acta*, 1954, **37**, 2207.

265. *Esterification by Sulphuric Acid.*

By (the late) Gwyn Williams and D. J. Clark.

Velocity and equilibrium constants for the solvolytic esterification of 2 : 4-dinitrobenzyl alcohol have been determined in 64—82% aqueous sulphuric acid at 25°, in 68—93% aqueous sulphuric acid at 0°, and (at 25°) in deutero-sulphuric acid–deuterium oxide solutions containing 69 and 76% of D_2SO_4.

Possible esterification mechanisms are discussed.

In previous measurements of the rates of the esterification of alcohols by concentrated aqueous sulphuric acid,[1,2,3] which established a number of the kinetic features of the reactions, the method of experiment has been to determine the sulphuric acid concentration in the reaction mixture; and therefore it has been necessary to avoid having the initial sulphuric acid concentration in too large excess over that of the alcohol. When the initial alcohol and sulphuric acid concentrations are not far apart, the acidity of the mixture inevitably changes as esterification proceeds.

[1] Deno and Newman, *J. Amer. Chem. Soc.*, 1950, **72**, 3852.
[2] Tian, *Bull. Soc. chim. France*, 1950, 1223.
[3] Dunnicliff and Butler, *J.*, 1920, **117**, 649; *J.*, 1921, **119**, 1384; Hamid, Singh, and Dunnicliff, *J.*, 1926, 1098.

The experiments which follow, on the sulphuric esterification of 2 : 4-dinitrobenzyl alcohol, differ in that we have always determined the *alcohol* concentration in samples of the reaction mixture by oxidation with potassium dichromate. It has thus been possible to keep the alcohol (and ester formed) at a low concentration in a sulphuric acid–water medium which retains a virtually constant composition throughout the reaction.

The Esterification Equilibrium.—The rate of sulphuric esterification of 0·1M-2 : 4-dinitrobenzyl alcohol is measurable in 64—82% sulphuric acid at 25° and in 68—93% sulphuric acid at 0°. The alcohol concentration falls to an equilibrium value, which remains constant indefinitely in solvents less acid than 82% sulphuric acid, but shows an apparent slow rise from a minimum in more concentrated acids. Simultaneously, in the most concentrated acids, the reaction mixture, normally colourless, becomes yellow and ultimately red. The apparent slow increase of alcohol concentration in the strongest acids, after esterification has reached equilibrium, may be attributed to an unidentified side reaction giving products which reduce the oxidising agent employed to determine the alcohol concentration. The analogous compound, benzyl alcohol, polymerises in concentrated sulphuric acid,[4] and 2 : 4-dinitrobenzyl chloride polymerises under the influence of alkali.[5] Tian [2] observed a formally analogous disturbance of the sulphuric esterification of alcohols $C_nH_{2n+1}\cdot OH$ with $n > 2$, and isolated hydrocarbons from the reaction mixtures.

The equilibrium concentration of ester, and the rates of approach to equilibrium, all fall with increasing water content of the system. The effect of medium composition on the esterification equilibrium is shown in Table 1. The results are expressed in terms of an equilibrium ratio, K, defined by equation (1), in which the suffixes i and e refer, respectively, to initial and equilibrium concentrations :

$$K = ([\mathrm{ROH}]_i - [\mathrm{ROH}]_e)/[\mathrm{ROH}]_e = [\mathrm{RO{\cdot}SO_3H}]_e/[\mathrm{ROH}]_e \quad . \quad . \quad . \quad (1)$$

Evidently, the calculated value of K is sensitive to error in the measurement of $[\mathrm{ROH}]_e$ if $[\mathrm{ROH}]_e \longrightarrow [\mathrm{ROH}]_i$. The error in K, caused by the unidentified side reaction, is considerable only in acids containing more than 87% of sulphuric acid.

The equilibrium ratio, K, of equation (1) naturally varies with the composition of the sulphuric acid–water reagent; but in a given sulphuric acid–water mixture, K changes only slightly for a four-fold variation of the initial alcohol concentration (Table 2).

Rates and Orders of Reaction.—Rates of esterification were generally measured by separate experiments (duplicated for each medium composition) in which the decrease of alcohol concentration with time was pursued to 80—85% of its equilibrium value. Over this range the quantity $\log (x_e - x)$ is accurately linear with time. The course of reaction may therefore be represented by equation (2*a*) (esterification and hydrolysis of first order with respect to alcohol and ester, respectively), equation (2*b*) (zero-order esterification and first-order hydrolysis), or equation (2*c*) (first-order esterification and zero-order hydrolysis),

$$2{\cdot}303 \log \{x_e/(x_e - x)\} = \begin{cases} (k_E + k_H)t \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a) \\ k_H t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2b) \\ k_E t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2c) \end{cases}$$

where x and x_e are, respectively, the ester concentrations at time t and at equilibrium, and k_E and k_H are, respectively, the first-order velocity coefficients for esterification and hydrolysis.

Of these three equations, (2*a*) is definitely to be preferred, because (2*b*) requires $[\mathrm{RO{\cdot}SO_3H}]_e$ to be independent of $[\mathrm{ROH}]_i$, and (2*c*) requires the same for $[\mathrm{ROH}]_e$. Neither is true in 76·79% sulphuric acid at 25° (Table 2). Instead, $[\mathrm{ROH}]_e \propto [\mathrm{ROH}]_i$, and $[\mathrm{RO{\cdot}SO_3H}] \propto [\mathrm{ROH}]_i$, as required by equation (2*a*). Further, the zero-order velocity coefficients calculated from (2*b*) and (2*c*) are proportional to $[\mathrm{ROH}]_i$, whereas the velocity coefficients derived from equation (2*a*) are nearly constant for a four-fold variation of $[\mathrm{ROH}]_i$ in 76·79% sulphuric acid at 25° (Table 2), k_H being a little more variable than k_E

[4] Shriner and Berger, *J. Org. Chem.*, 1941, **6**, 305.
[5] Friedländer and Cohn, *Monatsh.*, 1902, **23**, 546.

TABLE 1. *Variation of acid composition and temperature.*

Medium, H_2SO_4 (%)	Expt. no.	$[ROH]_o$ (M)	Esterifn. at equilm. (%)	K (mean)	10^4k_E (min.$^{-1}$)	10^4k_H (min.$^{-1}$)	10^4k_E, mean (min.$^{-1}$)	10^4k_H, mean (min.$^{-1}$)
(a) *Temperature*, 0°: $[ROH]_f$ = 0·1014 ± 0·0001M.								
68·03	115	0·0860	15·2	0·178	—	—	—	—
	114	—	—	—	0·524	2·94	0·521	2·93
	116	—	—	—	0·516	2·90		
	117	—	—	—	0·523	2·94		
72·72	102	0·0747	26·3	0·358	—	—	1·96	5·47
	100	—	—	—	1·97	5·50		
	103	—	—	—	1·95	5·43		
76·79	87	0·0587	42·1	0·727	—	—	7·12	9·81
	86	—	—	—	7·09	9·77		
	88	—	—	—	7·14	9·84		
	89	—	—	—	7·11	9·80		
80·71	112	0·0388	61·8	1·62	—	—	26·2	16·2
	111	—	—	—	26·2	16·2		
	113	—	—	—	26·2	16·2	—	—
82·20	105	0·0310	69·4	2·28	—	—	46·1	20·3
	104	—	—	—	46·0	20·2		
	106	—	—	—	46·1	20·3		
87·08	108	0·0125	87·7	7·12	—	—	268	37·7
	107	—	—	—	268	37·6	—	—
	109	—	—	—	269	37·7		
90·05	96	0·0076	92·5	12·4	—	—	682	55·3
	94	0·0075	92·6	—	692	56·0		
	95	—	—	—	673	54·5		
92·91	98	0·0050	95·1	19·4	—	—	1490	77·1
	97	—	—	—	1500	77·4		
	99	—	—	—	1490	76·8		
(b) *Temperature*, 25°: $[ROH]_f$ = 0·1014 ± 0·0002M.								
64·56	78	0·0903	10·8	0·121	—	—	7·48	61·8
	79	—	—	—	7·40	61·2		
	80	—	—	—	7·57	62·5		
	81	—	—	—	7·47	61·7		
69·70	52	0·0820	19·0	0·235	—	—	31·3	133
	53	0·0820	19·0	—	31·1	133		
	51	—	—	—	31·6	134		
72·72	62	0·0745	26·5	0·0360	—	—	71·7	200
	60	0·0744	26·5	—	71·4	199		
	61	—	—	—	72·1	201		
74·64	65	0·0684	32·5	0·481	—	—	122	254
	63	0·0684	32·5	—	123	255		
	64	—	—	—	121	252		
76·79	59	0·0602	40·6	0·684	—	—	236	345
	57	0·0602	40·6	—	234	342		
	58	—	—	—	238	347		
78·56	40	0·0527	48·0	0·924	—	—	390	423
	56	0·0527	48·0	—	—	—		
	54	—	—	—	385	417		
	55	—	—	—	396	428		
82·20	82	0·0355	65·0	1·86	—	—	1260	676
	83	—	—	—	1260	677		
	84	—	—	—	1260	677		
	85	—	—	—	1250	673		
(c) *Temperature*, 35°: $[ROH]_f$ = 0·1014—0·1015M.								
76·79	90	0·0605	40·3	0·680	830	1220	832	1220
	91	0·0603	40·5	—	833	1220		
	92	0·0605	40·4	—	834	1230		

TABLE 2. *Reactions in 76·79% sulphuric acid at 25°.*

Expt. no.	$[ROH]_t$ (M)	Salt concn. (M)	$[ROH]_e$ (M)	Esterifn. at equilm. (%)	K (mean)	10^4k_E (min.$^{-1}$)	10^4k_H (min.$^{-1}$)	10^4k_E, mean (min.$^{-1}$)	10^4k_H, mean (min.$^{-1}$)
(a) *Variation of initial alcohol concentration.*									
68	0·0507	—	0·0304	40·0	0·667	231	346	233	349
66	0·0507	—	0·0304	40·0	—	234	351	—	—
67	0·0507	—	—	—	—	233	349	—	—
—	0·1014	(Table 1)	0·0602	40·6	0·684	—	—	236	345
71	0·2031	—	0·1196	41·1	0·698	234	336	236	337
69	0·2031	—	0·1198	41·0	—	235	336	—	—
70	0·2030	—	—	—	—	237	339	—	—
(b) *Effects of added salts.*									
—	0·1014	(Table 1)	—	40·6	0·684	—	—	236	345
72	0·1015	$KHSO_4$ 0·500	0·0605	40·4	0·677	229	338	229	338
73	0·1015		0·0605	40·4	—	229	338	—	—
74	0·1015		0·0605	40·4	—	228	336	—	—
75	0·1014	$(NH_4)_2SO_4$ 0·500	0·0636	37·4	0·599	193	322	193	322
76	0·1014		0·0634	37·5	—	192	321	—	—
77	0·1014		0·0633	37·6	—	193	322	—	—

and accounting mainly for the small corresponding variation of K in Table 1. Of the various constants measured, the values of k_E are the most accurate.

For a given sulphuric acid–water composition, therefore, the rate of reaction is expressed by equation (3).

$$-d[ROH]/dt = k_E[ROH] - k_H[RO{\cdot}SO_3H] \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Variations of Rate with Sulphuric Acid–Water Compositions.—The individual velocity coefficients, k_E and k_H, are derived from the graphically computed $(k_E + k_H)$ of equation (2*a*) and K of equation (1). The variations of k_E with sulphuric acid–water composition at 25° and 0° are given by equations (4) and (5), in which H_o is Hammett's acidity function :[6]

$$\log k_E\,(25°) = -0{\cdot}959H_o\,(25°) - 7{\cdot}775 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\log k_E\,(0°) = -1{\cdot}084H_o\,(25°) - 10{\cdot}071 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The numerical terms in these equations are calculated by the method of least squares. The accuracy of fit may be judged from Table 5. The values of H_o are not known at 0°, so equation (5) is significant only if the variation of H_o with sulphuric acid–water composition at 0° is assumed to be strictly parallel to that at 25°.

Salt Effects.—Added salts may affect the reaction rates by altering activity coefficients which appear in the rate equations and also by changing the acidity of the medium. The effect of 0·5M-potassium hydrogen sulphate is small, but that of 0·5M-ammonium sulphate is more considerable [Table 2(b)]. The SO_4^{2-} ion is a base in 76·79% sulphuric acid, which contains little of this ion.[7] If the added 0·5M-SO_4^{2-} ion undergoes the reaction $SO_4^{2-} + OH_3^+ \longrightarrow HSO_4^- + H_2O$, then, from equation (6) which is due to Deno and Taft,[8] *viz.* :

$$H_o = -6{\cdot}66 + \log X_{H_2O}/X_{OH_3^+} + 1{\cdot}67 + \log f_{H_2O} \quad . \quad . \quad . \quad . \quad (6)$$

it may be estimated (without allowance for any change in f_{H_2O}) that 0·5M-ammonium sulphate alters H_o by +0·05, and hence, from equation (4), reduces k_E from 0·0236 to 0·021, the observed fall being to 0·019. The change in H_o is thus nearly great enough to account for the small retardation of esterification.

The effect of added salts on the rate of esterification is much less than it is on rates of reactions (such as nitration) which run parallel to the f_o acidity function.[9]

[6] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827.
[7] Young, *Rec. Chem. Progr.*, 1951, Spring Issue, p. 81.
[8] Deno and Taft, *J. Amer. Chem. Soc.*, 1954, **76**, 244.
[9] *E.g.*, Williams and Simkins, *J.*, 1953, 1386.

Effect of Temperature.—The Arrhenius parameters, calculated from the results of Table 1, are shown in Table 3.

TABLE 3. *Parameters of equation* $k_1 = Ae^{-E/RT}$.

		Esterification		Hydrolysis	
H_2SO_4 (%)	Temp.	$10^{-12}A$ (sec.$^{-1}$)	E (kcal./mole)	$10^{-12}A$ (sec.$^{-1}$)	E (kcal./mole)
72·72	0·00—25·05°	1·3	23·23	3·6	23·23
76·79	0·00—35·01	1·8	22·72	4·2	23·01
82·20	0·00—25·05	0·95	21·35	4·4	22·64

Reactions in Deuterosulphuric Acid.—Both esterification and ester hydrolysis are faster in deuterosulphuric acid than in sulphuric acid (Table 4). An analogy to this result for hydrolysis of the sulphuric ester exists in the faster, acid-catalysed hydrolyses of some carboxylic esters in deuterium oxide than in water.[10] Faster reaction by a deuterated

TABLE 4. *Esterification by deuterosulphuric acid at 25°.*

$[ROH]_t$ = 0·1018—0·1019M

Medium : D_2SO_4 (%)	Expt. no.	$[ROH]_t$ (M)	Esterifn. at equilm. (%)	K (mean)	10^4k_E (min.$^{-1}$)	10^4k_H (min.$^{-1}$)	k_ED/k_EH	k_HD/k_HH
69·17	122	0·0779	23·5	0·306	83·4	272	—	—
	123	0·0780	23·4	—	84·9	277	—	—
				Mean	84·1	275	1·90	1·74
75·54	120	0·0576	43·5	0·765	451	590	—	—
	121	0·0579	43·2	—	439	574	—	—
				Mean	445	582	1·74	1·63

reagent is an indication that a rapidly established proton-transfer equilibrium precedes the rate-determining step in the process.[11]

State of the Reagents.—The 64·5—82·2% sulphuric acid used for the experiments at 25° contains water in initial molecular excess over sulphuric acid, and the concentration of molecular sulphuric acid present is small.[7] The condition of alcohol and ester in this solvent range cannot be certain. Cryoscopy shows that ester may exist to a small extent as $RO{\cdot}SO_3H_2^+$ (or R^+) in anhydrous sulphuric acid,[12] but does not reveal clearly that an alcohol ROH forms ROH_2^+, because of further reactions with sulphuric acid.[13] 2 : 4-Dinitrobenzyl alcohol must be a weaker base than ethyl alcohol, which is considered to be a weaker base than water.[14] In 64·5—82·2% sulphuric acid, the alcohol may be assumed to exist predominantly as ROH, while the ester may be largely [15] present as $RO{\cdot}SO_3^-$.

Reaction Mechanisms.—With alcohol in small initial concentration, both esterification and ester hydrolysis are solvolytic, and the results of Table 1 establish no reaction order with respect to the solvent component. The effective reacting species cannot be identified unequivocally; and multiplicity of mechanisms, or change of mechanism with changing acid composition, cannot be rigidly excluded. Nevertheless, the variation of esterification rate is given, for the whole range of acid compositions investigated, by equation (4) at 25° and equation (5) at 0°. The *simplest* interpretation of equation (4) is that the rate-determining step in esterification is a unimolecular decomposition of the conjugate acid of an initial reagent.[16] A rate-determining step ROH ⟶ R^+ is improbable, for Deno and Newman have argued convincingly against alkyl–oxygen fission in sulphuric esterification (*a*) that sulphuric acid esterifies (+)-butan-2-ol with retention of configuration, though the

[10] Hornel and Butler, *J.*, 1936, 1361.
[11] Bell, "Acid–Base Catalysis," Oxford Univ. Press, 1941, p. 145.
[12] Gillespie, *J.*, 1950, 2542.
[13] Newman, Craig, and Garrett, *J. Amer. Chem. Soc.*, 1949, **71**, 869; 1950, **72**, 163; Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 40.
[14] Braude, *J.*, 1948, 1971; Braude and Stern, *ibid.*, p. 1976.
[15] Cf. Deno and Newman, *J. Amer. Chem. Soc.*, 1951, **73**, 1920.
[16] Zucker and Hammett, *ibid.*, 1939, **61**, 2791; Long and Purchase, *ibid.*, 1950, **72**, 3272; McIntyre and Long, *ibid.*, 1954, **76**, 3240.

ester is then racemised, and (*b*) that *neo*pentyl alcohol forms *neo*pentyl hydrogen sulphate without molecular rearrangement.[17]

A possible reaction sequence for the solvolytic esterification is

$$ROH + HSO_4^- \longrightarrow Q \text{ fast}; [Q] \sim [ROH]_{st} \quad . \quad . \quad . \quad . \quad (7)$$

$$Q + H^+ \rightleftharpoons QH^+ \text{ fast}; [Q] \gg [QH^+] \quad . \quad . \quad . \quad . \quad (8)$$

$$QH^+ \longrightarrow RO{\cdot}SO_3^- \text{ slow} \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

in which the whole of the alcohol forms a complex, Q, with a component of the acid; a small proportion of Q exists as QH^+; and the rate-determining step is a unimolecular decomposition of QH^+ to form ester. From equations (7)—(9), in which $[ROH]_{st}$ stands for the stoicheiometric concentration of 2 : 4-dinitrobenzyl alcohol, the rate of esterification, r_E, is given by

$$r_E = k_E[ROH]_{st} = k_E^\circ[QH^+]f_{QH^+}/f_{tr} = k_E^\circ K_8[Q]a_{H^+}f_Q/f_{tr} \quad . \quad . \quad (10)$$

In (10), K_8 is the equilibrium constant of (8) and k°_E is supposed independent of the acid composition. The transition state of (9) is akin to the conjugate acid of Q, so that (10) gives (11):

$$\log k_E + H_0 = \log k_E^\circ + \log K_8 \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

in agreement with equation (4).

Although a unimolecular mechanism offers the simplest interpretation of the solvolytic esterification results, bimolecular mechanisms cannot be excluded,[18] since the range of sulphuric acid–water compositions in which k_E can be measured at 25° is not very wide and lies in a region [8] in which individual activity coefficients are not constant and in which concentrations of bisulphate and oxonium ions probably do not vary by more than some 30%, though the concentration of molecular water may change 5-fold and the small concentration of molecular sulphuric acid (which cannot be accurately estimated) may change very markedly. Deno and Newman [1] found that their results with equimolar proportions of alcohol and sulphuric acid were best represented by the equation:

$$d[RO{\cdot}SO_3H]/dt = k[ROH][H_2SO_4]a_{H^+}$$

Bimolecular esterification could occur between either ROH, or ROH_2^+, and HSO_4^-, H_2SO_4, $H_3SO_4^+$, or HSO_3^+. However, $H_3SO_4^+$ and HSO_3^+ can be excluded because reaction of alcohol with these would require log k_E to run parallel to $2H_0$ and $(H_0 + J_0)$ respectively, contrary to equation (4). Deno and Newman regarded the pairs $(ROH_2^+ + H_2SO_4)$, $(ROH + H_2SO_4)$, or $(ROH + H_2SO_4^+)$ as being the most probable. The reaction sequence:

$$HSO_4^- + H^+ \rightleftharpoons H_2SO_4 \text{ fast}; [HSO_4^-] \gg [H_2SO_4] \quad . \quad . \quad . \quad (12)$$

$$H_2SO_4 + ROH \longrightarrow RO{\cdot}SO_3H + H_2O \text{ slow} \quad . \quad . \quad . \quad . \quad . \quad (13)$$

leads to the equation:

$$\log k_E = \log k_E^\circ + \log a_{H_2SO_4} + \log f_{ROH}/f_{tr} \quad . \quad . \quad . \quad . \quad (14)$$

in which k_E° is supposed independent of medium and f_{tr} refers to the transition state. If the ratio f_{ROH}/f_{tr} (referring to two neutral species) is supposed independent of medium, then:

$$\log k_E - \log a_{H_2SO_4} = \text{const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

Alternatively:

$$\log k_E = \log k_E^\circ + \log K_{12} + \log [HSO_4^-] - H_0 + \log (f_{ROH}f_{H_2SO_4}/f_{tr}) \quad . \quad (16)$$

[17] Whitmore and Rothrock, *J. Amer. Chem. Soc.*, 1932, **54**, 3432.
[18] Cf. Schubert and Zahler, *ibid.*, 1954, **76**, 1; Schubert, Donohue, and Gardner, *ibid.*, p. 9.

if products of the type $f_{BH^+}f_{HSO_4^-}/f_Bf_{H_2SO_4}$ are invariant throughout the medium range. Only if the expression in activity coefficients in (16) is also invariant is equation (17) true :

$$\log k_E - \log [HSO_4^-] + H_o = \text{const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

The same expression may be derived from the reaction sequence :

$$ROH + H^+ \rightleftharpoons ROH_2^+ \text{ fast, } [ROH] \gg [ROH_2^+] \quad . \quad . \quad (18)$$

$$ROH_2^+ + HSO_4^- \longrightarrow RO{\cdot}SO_3H + H_2O \text{ slow} \quad . \quad . \quad . \quad . \quad . \quad (19)$$

if the product $f_{ROH_2^+}f_{HSO_4^-}/f_{tr}$ is invariant. Reaction between H_2SO_4, formed as in (12), and ROH_2^+, formed as in (18), requires $\log k_E$ to run parallel to a multiple of H_o, contrary to equation (4).

Constancy of the sums on the left-hand side of equations (11) and (17) is tested in Table 5(*a*) and (*c*) respectively, the concentrations of the medium constituents being calculated from mole fractions X_{H_2O} derived by Deno and Taft [8] on the supposition that $X_{OH_3^+}X_{HSO_4^-}/X_{H_2O}X_{H_2SO_4} = 50$ at 25°. Equation (15) is tested in Table 5(*b*) from values of $a_{H_2SO_4}$ at 25°, calculated by Abel.[19]

TABLE 5.

H_2SO_4 (%)	H_o (25°)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)
64·56	−4·84	−7·97	−8·19	−8·96	−7·77	—
68·03	−5·29	—	—	—	—	−10·02
69·70	−5·50	−8·00	−8·45	−9·06	−7·78	—
72·72	−5·88	−8·03	−8·56	−9·11	−7·78	−10·08
74·64	−6·11	−8·03	−8·63	−9·13	−7·78	—
76·79	−6·40	−8·03	−8·68	−9·15	−7·77	−10·09
78·56	−6·63	−8·04	−8·73	−9·17	−7·77	—
80·71	−6·93	—	—	—	—	−10·09
82·20	−7·17	−8·07	−8·74	−9·20	−7·78	−10·11
87·08	−7·85	—	—	—	—	−10·08
90·05	−8·18	—	—	—	—	−10·03
92·91	−8·50	—	—	—	—	−10·04

(*a*) $\log k_E$ (25°) + H_o. (*b*) $\log k_E$ (25°) − $\log a_{H_2SO_4}$.
(*c*) $\log k_E$ (25°) − $\log [HSO_4^-]$ + H_o.
(*d*) $\log k_E$ (25°) + $0{\cdot}959H_o$.
(*e*) $\log k_E$ (0°) + $1{\cdot}084H_o$.

Equations (15) and (17), referring to bimolecular mechanisms, have no advantage over (11) in reproducing the experimental equation (4); but they cannot be rejected (or accepted) out of hand in view of the possible variations of activity coefficients with changing acid composition. The results at 0° [Table 1(a)] extend to acid compositions made up with sulphuric acid in molecular excess over water; but they cannot be tested satisfactorily, because H_o has not been measured at 0° and the concentrations of solvent constituents are doubtful.

EXPERIMENTAL

Materials.—2 : 4-Dinitrobenzyl alcohol was prepared [20] from 2 : 4-dinitrobenzyl chloride (either a commercial product, or a sample made by nitration of *p*-nitrobenzyl chloride [21]), by conversion into the acetate and hydrolysis of this with 50% sulphuric acid at 120°. The product was crystallised from water, methanol, and benzene (twice), and had m. p. 115·5—116° (Found : C, 42·7; H, 3·25; N, 14·25. Calc. for $C_7H_6O_5N_2$: C, 42·4; H, 3·05; N, 14·15%). Analysis by dichromate oxidation gave 99·9% alcohol.

The sulphuric acid–water mixtures were analysed by titrating samples from a weight-burette (with methyl-orange–xylene-cyanol indicator) against 0·8N-sodium hydroxide, this being standardised against N-hydrochloric acid, itself standardised against standard potassium iodate and checked occasionally against standard sodium carbonate and also gravimetrically. Six samples of each medium were analysed; *e.g.*, medium S9 gave 64·59, 64·54, 64·55, 64·58,

[19] Abel, *J. Phys. Chem.*, 1946, **50**, 260.
[20] Friedländer and Cohn, *Monatsh.*, 1902, **23**, 546; *Ber.*, 1902, **35**, 1266.
[21] Escales, *Ber.*, 1904, **37**, 3599.

64·54, 64·57, mean 64·56% sulphuric acid. The mixtures maintained their composition when stored in glass-stoppered bottles; *e.g.*, medium S11, when prepared, was 72·73, and, after 8 months, was 72·71% sulphuric acid.

Deuterosulphuric acid–deuterium oxide reagents were prepared by distilling sulphur trioxide (itself distilled from oleum) into heavy water (d_4^{20} 1·10513) containing 99·74% of D_2O, in all-glass apparatus.[22] The products were analysed by titration with 0·4N-alkali; *e.g.*, one medium gave 75·49, 75·53, 75·55, 75·55, 75·55, 75·55, mean 75·54% D_2SO_4.

Inorganic salts used were of "AnalaR" quality and were dried at 110° before use, except ammonium sulphate, which was dried at 60—65°.

Reaction Mixtures.—100 c.c. of sulphuric acid reagent, at thermostat temperature, were transferred from a weighed standard flask to the 250 c.c. stoppered reaction flask. After a standard drainage time of 30 sec., the empty standard flask was re-weighed, to determine the exact amount of sulphuric acid used. A weighed amount of the alcohol (2 g.) was introduced from a cone-cap fitting the flask neck. Dissolution of the alcohol (accelerated by shaking) required a time (from <1 min. in 82% H_2SO_4 at 25° to over 4 hr. in 68% H_2SO_4 at 0°) short compared with the whole time of reaction. A small initial timing error was unimportant, since velocity coefficients were computed graphically. When dissolution was complete, the flask was placed under vacuum to remove air bubbles, after which samples (10 c.c.) were extracted by pipette at timed intervals. Volumetric apparatus was calibrated for the liquids used.

For experiments in deuterosulphuric acid, only 25 c.c. of reaction mixture were used and 2 c.c. samples were extracted. The loss in accuracy was small, *e.g.*, in 76·79% H_2SO_4 the standard method gave K = 0·684, k_E = 0·0236, and the modified procedure yielded K = 0·666, k_E = 0·0238.

Analytical Method.—The sample of reaction mixture was run on to a partly frozen mixture (cooled externally; for crushed ice in the reagent introduced oxidisable impurity) of 25 ml. of 0·32N-potassium dichromate with enough water to bring the final acid concentration to 6N. After 18 hr. the solution was titrated with 0·2M-ferrous ammonium sulphate (made up in 0·8N-sulphuric acid), with three drops of ferroin indicator.

For this adaptation of the dichromate oxidation method to the determination of 2 : 4-dinitrobenzyl alcohol, in presence of its sulphuric ester, 6N-sulphuric acid was found to be the optimum oxidation medium, allowing fast enough oxidation of the alcohol with minimal hydrolysis of the ester. Oxidation of the alcohol was complete after 3 hr. at 15°; but longer oxidation periods were more convenient for routine analyses. Twenty-two analyses, in the absence of ester, on 0·02—0·2 g. samples of 2 : 4-dinitrobenzyl alcohol (corresponding to concn. 0·01—0·1M in a reaction mixture), oxidised in 6N-acid at 13—18° for 16—216 hr., gave results within ±0·3% of the theoretical. To test the effect of ester, 0·1016M-alcohol was allowed to come to the esterification equilibrium (202 min.) in 87·08% sulphuric acid at 0°. Samples were then analysed for alcohol with exposure to the oxidant in 6N-acid, at 13—18°, for different times (Table 6).

TABLE 6.

Oxidation time (hr.)	18·9	19·0	44·4	44·8	68·9	90·8	91·0	215	217
10^2[ROH] (M)	1·28	1·27	1·33	1·33	1·38	1·40	1·41	1·60	1·60
10^2[$RHSO_4$] (M)	8·88	8·89	8·83	8·83	8·78	8·75	8·75	8·56	8·56

From these figures it may be inferred that 0·5% of the ester present is hydrolysed in 24 hr. at 15°, and that hydrolysis during the oxidation period of 18 hr. can only affect the measured alcohol concentration appreciably when ester is present in great excess over alcohol. When this was so, the temperature was held below 10° during oxidation.

Equilibrium Constants.—The equilibrium concentration of alcohol was usually measured, for each medium, by a special experiment (see Table 1) continued long enough (0·8—33 hr. at 25°; 0·7—427 hr. at 0°) to allow for 4—9 determinations of the steady alcohol concentration. *E.g.*, in expt. 65 seven analyses, after reaction periods ranging from 3½ to 11 hr., returned $[ROH]_e$ = 0·0685, 0·0685, 0·0684, 0·0683, 0·0683, 0·0683, 0·0683, mean 0·0684.

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[22] Best and Wilson, *J.*, 1946, 239; Bonner, Bowyer, and Williams, *J.*, 1953, 2650.

266. *The* Hg–Hg *Bond Length in the Mercurous Ion. Part I. The Crystal Structure of Mercurous Nitrate Dihydrate.*

By D. Grdenić.

Crystals of mercurous nitrate dihydrate, $Hg_2(NO_3)_2.2H_2O$, are monoclinic with space group C_{2h}^5-$P2_1/n$. The unit cell, of dimensions $a = 8{\cdot}64$ Å, $b = 7{\cdot}52$ Å, $c = 6{\cdot}30$ Å, $\beta = 103°48'$, contains two formula units. The structure was determined with the aid of Patterson and Fourier–Bragg [010] and [100] projections, and by trial-and-error methods. The termination-of-series effect was quite large, so that the positions of the water molecules and nitrate ions could not be obtained accurately. The mercury atoms are linked in pairs across centres of symmetry, the distance between them being $2{\cdot}54 \pm 0{\cdot}01$ Å. Each mercury atom has three oxygen atoms as nearest neighbours, two belonging to the nitrate ion and the third to the water molecule at distances of 2·42, 2·40, and 2·15 Å, respectively. The close approach of 2·15 Å of the water molecule to the mercury atom gives evidence for a co-ordination link, resulting in the formation of an oxonium ion $[H_2O{\cdot}Hg{\cdot}Hg{\cdot}OH_2]^{2+}$.

Little is known about the crystal chemistry of mercurous compounds, the only crystal structures so far determined being those of mercurous chloride, bromide, and iodide.[1] These structures consist of linear X–Hg–Hg–X molecules with Hg–Hg distances of 2·53 Å in the chloride, 2·58 Å in the bromide, and 2·69 Å in the iodide. This apparent dependence of the Hg–Hg distance on the nature of the anion deserved further investigation and we have examined the mercurous nitrate dihydrate and fluoride. In the present communication the results of the crystal analysis of the former are reported and Part II (following paper) deals with the structure of mercurous fluoride.

Experimental.

Crystallographic and X-Ray Data.—The crystals were prepared from a warm saturated solution of mercurous nitrate dihydrate in dilute nitric acid. When the solution was slowly cooled to room temperature the crystals obtained were usually prismatic, elongated in the [100] direction. By rapid cooling crystals in the form of plates parallel to (010) with well-developed (101) faces were formed. Crystals of both these habits had already been described and examined crystallographically by Marignac.[2] Another form, not described by Marignac, was also very occasionally obtained: these were prisms elongated along [010].

In the present paper all crystallographic data are referred to the axes chosen by Marignac. The unit cell as determined from oscillation photographs and goniometer measurements has the dimensions: $a = 8{\cdot}64$ Å, $b = 7{\cdot}52$ Å, $c = 6{\cdot}30$ Å, $\beta = 103°48'$. The axial ratios $a : b : c = 1{\cdot}149 : 1 : 0{\cdot}838$ agree well with the values $a : b : c = 1{\cdot}1503 : 1 : 0{\cdot}8334$ and $\beta = 103°47{\cdot}5'$ given by Marignac. Systematic extinctions were observed only for $h0l$ spectra with $h + l$ odd and for $0k0$ with k odd. The space group is therefore C_{2h}^5-$P2_1/n$. Two formula units being assumed in the unit cell, the calculated density is 4·683 in agreement with the value of 4·785 given by Playfair and Joule.[3]

Intensity Measurements.—In view of the large absorption power ($\mu = 750$ cm.$^{-1}$ for Cu-$K\alpha$ radiation) it was very important to choose a crystal whose shape was suitable for easy evaluation of the absorption correction. For recording $0kl$ spectra a plate-shaped crystal of convenient size was cut with a razor-blade parallel to the b axis. The crystal specimens were preserved from decomposition during photography by a thin coating of nitrocellulose laquer. Nickel-filtered Cu-K radiation was used, and all possible ($0kl$) and ($h0l$) spectra were recorded on double-film Weissenberg photographs. The relative intensities of the reflexions were determined from the optical densities of the spots measured with a microdensitometer and corrected by means of the characteristic curve of the film. The correction for absorption was made very carefully by applying formulæ described previously.[4] The ratios of the smallest absorption factor to the

[1] Havighurst, *J. Amer. Chem. Soc.*, 1926, **48**, 2113.
[2] Marignac, *Ann. Chim. Phys.*, 1849, [iii], **27**, 332.
[3] Playfair and Joule, *Mem. Chem. Soc.*, 1845, **2**, 401.
[4] Grdenić, *Acta Cryst.*, 1952, **5**, 283.

largest were 1 : 60 and 1 : 29 for the *h*0*l* and 0*kl* reflexions, respectively. The corrections for polarization and Lorentz factors were made in the usual way. The number of *h*0*l* and 0*kl* reflexions observed was 64 and 49 respectively.

FIG. 1. *Electron-density projection of mercurous nitrate dihydrate along* (*a*) [010], (*b*) [100], *with superimposed atomic positions. The contacts, water–mercury, nitrate–nitrate ion, water–nitrate ion, are represented by broken lines with distances in* Å. *Contours are drawn on an arbitrary scale. Only alternate levels are drawn on the mercury-atom peaks.*

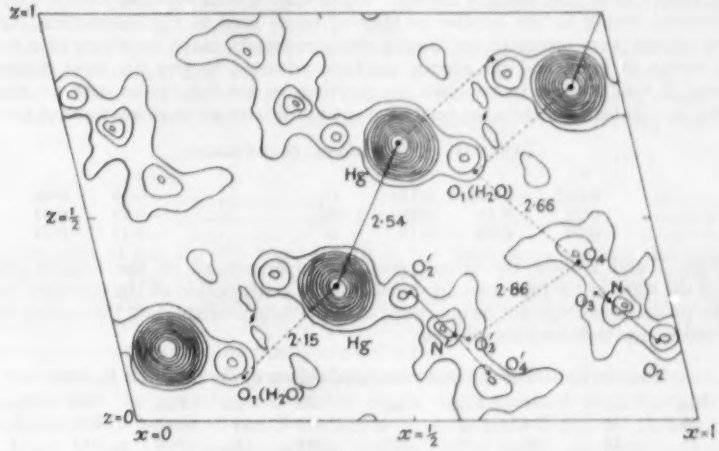
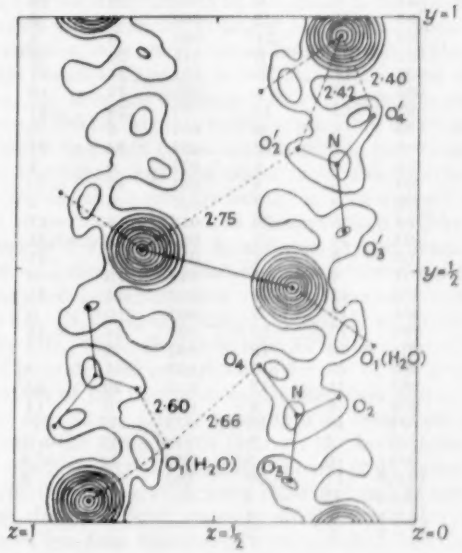


FIG. 2.



Determination of the Structure.—By using the mercury parameters $x_{Hg} = 0{\cdot}085$ and $z_{Hg} = 0{\cdot}189$, evaluated from the (*x*, *z*) Patterson projection, the signs for observed F(*h*0*l*) were calculated, with neglect of the contributions of light atoms. The Fourier projection on (010) is shown in Fig. 1. The water molecule and nitrate ion peaks are also, though badly, resolved. The parameter y_{Hg} was easily obtained by trial-and-error methods, the best agreement between observed

and calculated intensities being obtained by taking $y_{Hg} = 0{\cdot}04$. By means of these y_{Hg} and z_{Hg} parameters, the signs of the observed $F(0kl)$ were computed and the Fourier projection along [100] evaluated (Fig. 2). The water-molecule peak did not appear at the same position in both projections, the difference being about 0·2 Å in the z co-ordinate. The nitrate-ion peaks were also resolved, but not as clearly as in the [010] projection. The oxygen peak near to the mercury peak was accompanied by a broad, low, spurious peak.

The shapes and positions of the light-atom peaks appeared to be considerably influenced by diffraction effects from the mercury atoms. These effects were especially pronounced in the [100] projection, owing to the smaller number of terms used in the summation. Models of possible structures were projected on to both electron-density maps by means of a mirror and a parallel source of light, and the atomic positions adjusted to give the most reasonable fit. In this way, it was possible to establish the positions of the light atom with an accuracy of about ±0·1 Å. Table 1 contains the final atomic co-ordinates given in fractions of the unit-cell

TABLE 1. *Final atomic co-ordinates.*

	x	y	z		x	y	z
Hg	0·087	−0·038	0·188	O_2	−0·13	0·08	0·31
O_1 (H_2O)	0·21	0·34	0·10	O_4	−0·15	0·31	0·39
O_3	−0·04	0·25	0·19	N	−0·11	0·22	0·29

edges. Figs. 1 and 2 show the atomic positions superimposed on the Fourier projections. Because all the signs of the reflexions are defined by the contribution of the mercury atom alone, the Fourier projections could not be improved with the data available and the further refinement of the structure was therefore not possible.

TABLE 2. *Observed and calculated values of the structure factors.*

$h0l$	$F_{obs.}$	$F_{calc.}$	$h0l$	$F_{obs.}$	$F_{calc.}$	$0kl$	$F_{obs.}$	$F_{calc.}$	$0kl$	$F_{obs.}$	$F_{calc.}$
200	26	30	$\bar{4}08$	2	5	002	48	−45	073	0	0
400	38	−34	$\bar{5}01$	16	−26	004	0	− 2	083	2	4
600	26	−31	$\bar{5}03$	23	20	006	15	11	093	1	4
800	6	− 5	$\bar{5}05$	15	− 8	020	37	44	014	9	8
10,0,0	5	6	$\bar{5}01$	0	6	040	22	28	024	0	2
101	14	− 4	$\bar{5}03$	15	22	060	0	2	034	22	16
103	30	−37	$\bar{5}05$	18	−21	080	6	− 5	044	3	3
105	42	24	$\bar{5}07$	8	6	011	20	23	054	27	17
107	10	− 7	$\bar{6}02$	17	20	021	21	−27	064	2	0
$\bar{1}01$	55	49	$\bar{6}04$	5	− 4	031	12	16	074	16	12
$\bar{1}03$	30	−47	$\bar{6}02$	23	18	041	28	−37	084	0	0
$\bar{1}05$	15	18	$\bar{6}04$	3	6	051	5	6	015	22	21
$\bar{1}07$	2	1	$\bar{6}06$	9	−12	061	24	24	025	6	4
202	59	−63	$\bar{7}01$	0	4	071	0	− 1	035	16	15
204	35	30	$\bar{7}03$	8	8	081	10	−10	045	6	6
206	5	− 4	$\bar{7}05$	0	7	091	0	− 2	055	5	4
$\bar{2}02$	17	24	$\bar{7}01$	24	−26	012	16	−17	065	8	4
$\bar{2}04$	27	−36	$\bar{7}03$	18	23	022	33	−33	075	0	1
$\bar{2}06$	16	19	$\bar{7}05$	5	− 7	032	23	−17	016	5	− 3
$\bar{2}08$	4	− 7	$\bar{7}07$	4	− 4	042	16	−19	026	13	10
301	37	−37	$\bar{8}02$	13	11	052	23	−18	036	12	7
303	14	11	$\bar{8}04$	15	− 7	062	0	0	046	8	5
305	7	6	$\bar{8}02$	10	−10	072	14	−11	056	10	− 7
307	10	− 7	$\bar{8}04$	16	16	082	2	3	066	2	0
$\bar{3}01$	38	45	$\bar{8}06$	12	− 9	092	1	− 5	017	4	− 4
$\bar{3}03$	11	8	901	11	13	013	39	−40	027	5	− 5
$\bar{3}05$	10	−11	903	4	− 4	023	10	14	037	4	− 3
$\bar{3}07$	11	11	$\bar{9}01$	10	−13	033	32	−27	047	8	− 5
402	4	− 1	$\bar{9}03$	2	3	043	15	− 6			
404	20	18	$\bar{9}05$	6	5	053	12	− 9			
406	17	−10	$\bar{10},0,2$	11	−10	063	5	8			
$\bar{4}02$	46	46	$\bar{10},0,4$	12	7						
$\bar{4}04$	36	−27	$\bar{11},0,1$	0	1						
$\bar{4}06$	2	3	$\bar{11},0,3$	5	− 5						

Structure factors were calculated by using values for the atomic scattering factors given in "Internationale Tabellen,"[5] multiplied by an average temperature factor with $B = 4$ Å^2.

Nevertheless, a test of the reliability of the atomic co-ordinates may be obtained by comparing the observed and the calculated structure amplitude. This is done in Table 2. At the

[5] "Internationale Tabellen zur Bestimmung der Kristallstrukturen," Borntraeger, Berlin, 1935, Vol. II, p. 571.

first stage of the analysis, when the structure amplitudes were calculated for the mercury atom alone, the reliability index $R = \sum||F_o| - |F_c||/\sum|F_o|$ was 0·26. For the complete structure $R = 0{\cdot}25$ for the $h0l$ terms and 0·22 for the $0kl$ terms. The large disagreement for some reflexions may have been caused by uncertainty in estimation of the absorption factor when the formulæ could not be applied, *e.g.*, when the incident angle of the *X*-ray beam to the crystal face was near zero, or when a rough edge caused by cutting of the crystal was reflecting. Further, for weak or very weak reflexions the calculated contributions of light atoms were generally of the opposite sign to that of the mercury atom; this incidentally proved the reliability of the co-ordinates for oxygen and nitrogen given in Table I.

The accuracy of the co-ordinates of mercury was estimated by Cruickshank's formula[6] for the standard deviation $\sigma(x)$ and $\sigma(z)$ of a peak position in an electron-density map. The result obtained was $\sigma(x) = \sigma(z) = 0{\cdot}005$ Å. Owing to the centre-of-symmetry relation between mercury atoms the standard deviation for the value obtained for the Hg–Hg bond length is $\sigma(d_{Hg-Hg}) = 0{\cdot}01$ Å.

Discussion

Determination of the Hg–Hg bond length in the mercurous ion was the main aim of this investigation. The value obtained, 2·54 ± 0·01 Å, is almost equal to that found previously [1] for the Hg–Hg distance in crystals of mercurous chloride. Further discussion of this value does not seem to be very profitable until more data on the Hg–Hg bond length in various mercurous compounds are collected.

The positions of the light atoms obtained define the structure in a satisfactory way. The distances and the co-ordination of the atoms are consistent with known crystallochemical facts. The length of the N–O bonds in the nitrate ion is 1·1 Å and the angle between them about 120°, which, within the estimated limits of error, correspond to recorded values (1·20 Å and 120°).

The light-atom part of the structure can be described in the following way: The nitrate ions related by a two-fold screw axis are arranged in infinite chains parallel to the *b* axis. The contact distance between each nitrate ion and a neighbour in the same chain, measured by the oxygen–oxygen distance (O_4–O_3'), is 2·86 Å. There is no direct contact between the nitrate-ion chains, but they are linked across by means of water molecules at rather short contact distances of 2·60 Å from each chain, probably by means of hydrogen bonds. From each water molecule two such bonds are directed to two different nitrate ions at an angle of 110°. Thus, the nitrate ions and water molecules together form a frame-work, in the holes of which the mercurous ions are located in such a way that each mercury atom is surrounded by four atoms, namely the next mercury atom at 2·54 Å, two oxygen atoms of the same nitrate ion at 2·40 and 2·42 Å, and one oxygen atom belonging to a water molecule at a distance of 2·15 Å. The short distance between the mercury atom and the water molecule suggests a polarisation effect of the mercurous ion on the water molecule, and that an oxonium ion, $[H_2O–Hg–Hg–OH_2]^{2+}$, probably exists in the crystal structure. The bond angle Hg–Hg–OH_2, which should be 180° if the bond were truly covalent, is about 160°. This departure indicates the remarkable influence of the neighbouring nitrate ion, resulting in the formation of the hydrogen bonds described above. It may be assumed that such an oxonium ion occurs also in a solution of mercurous nitrate. A short co-ordination bond of nearly the same length (2·21 Å) has been shown to exist in mercury diethylene oxide.[7] A much shorter, covalent Hg–O bond (2·03 Å) was found recently in the crystal structure of tri(chloromercury)oxonium chloride [8] and in trimercuric oxychloride.[9]

The values for the distances from mercury to the nitrate-oxygen atoms (2·40 and 2·42 Å) are in both cases less than the sum of corresponding van der Waals radii (1·50 Å for mercury and 1·40 Å for oxygen), so that they also suggest polarization caused by the mercurous ion. It is interesting that this distance is nearly equal to the sum of ionic

[6] Cruickshank, *Acta Cryst.*, 1949, **2**, 65.
[7] Grdenić, *ibid.*, 1952, **5**, 367.
[8] Scavnicar and Grdenić, *ibid.*, 1955, **8**, 275.
[9] Scavnicar, *ibid.*, p. 379.

radii if the values of 1·10 Å, the generally accepted value for the radius of the mercuric ion, and 1·35 Å for the oxygen are used.

The author is greatly indebted to Dr. B. Oughton (Chemical Crystallography Laboratory, Oxford) for valuable discussion and help in improving the light-atom co-ordinates and in preparing the manuscript. Thanks are offered to the Physical Institute, Faculty of Science, Zagreb, and to Institut Rudjer Bosković, Zagreb, where most of the experimental work was performed.

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267. *The* Hg–Hg *Bond Length in the Mercurous Ion. Part II.* The Crystal Structure of Mercurous Fluoride.*

By D. Grdenić and C. Djordjević.

The crystal structure of mercurous fluoride has been determined by the use of *X*-ray methods. The value 2·43 ± 0·04 Å has been obtained for the Hg–Hg bond length. It is proved that the Hg–Hg bond length in mercurous halides depends upon the nature of the halogen, decreasing in passing from the iodide *via* the bromide and chloride to the fluoride. The Hg–F distance is 2·13 ± 0·05 Å.

The crystal structures of mercurous chloride, bromide and iodide[1,2,3,4] have been previously determined, but the values for the atomic parameters given by Havighurst [2] are probably the most accurate, since they were obtained from Fourier series. All bond-lengths quoted in this paper are therefore based on Havighurst's data. According to them the Hg–Hg bond length in the mercurous ion increases on passing from calomel to mercurous bromide and iodide. The electronegativity of the halogens decreases as the series is ascended and therefore the mercury atoms would be expected to have smaller positive charges. On this simple conception the Hg–Hg bond length would be expected to decrease as the series is ascended. In fact it increases from fluoride to iodide.

To complete the series of Hg–Hg bond lengths for the mercurous halides it is necessary to determine the structure of mercurous fluoride. If the relation discussed above between the Hg–Hg bond length values and the nature of the anion is valid, the Hg–Hg distance in mercurous fluoride should be the shortest.

Ebert and Voitinek [5] have reported an examination of mercurous fluoride powder by *X*-ray-diffraction methods. They found that crystals of mercurous fluoride were tetragonal, with the space group $D_{4h}^{17} - I4/mmm$, and that the unit cell, of dimensions $a = 3{\cdot}66$, $c = 10{\cdot}90$ Å, contained two molecules. They concluded that mercurous fluoride was isostructural with the other mercurous halides.

Experimental

Preparation of the Specimen.—Mercurous fluoride was prepared by dissolving mercurous carbonate in hydrofluoric acid.[6] Attempts to obtain suitable single crystals from hydrofluoric acid solution failed. Thus all data were obtained from powder diffraction photographs. The specimen was prepared by sealing the well-ground material in a 0·3 mm. quartz capillary.

X-Ray Data.—The powder photographs were taken with a Unicam vacuum camera of 19 cm. diameter, with nickel-filtered Cu-*K* radiation. The unit cell and space group determined previously [5] were confirmed.

* Part I, preceding paper.

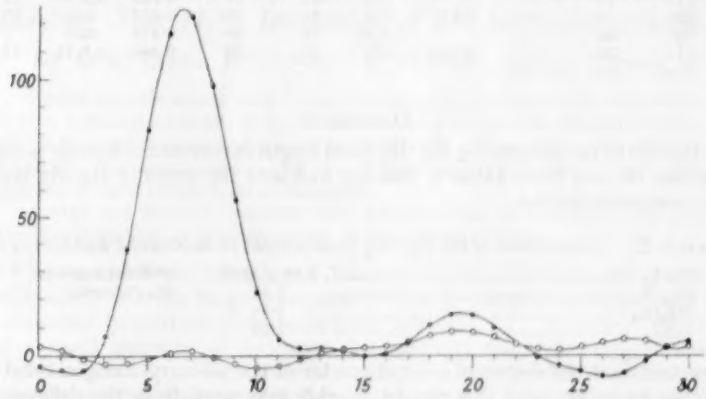
[1] Mauguin, *Compt. rend.*, 1925, **178**, 15.
[2] Havighurst, *J. Amer. Chem. Soc.*, 1926, **48**, 2113.
[3] Huggins and Magill, *ibid.*, 1927, **49**, 2357.
[4] Hylleraas, *Z. Physik*, 1926, **36**, 859.
[5] Ebert and Voitinek, *Z. anorg. Chem.*, 1933, **210**, 269.
[6] Henne and Renoll, *J. Amer. Chem. Soc.*, 1938, **60**, 1060.

Intensity Measurements.—The optical density of the diffraction lines was measured with a recording microdensitometer, and the relative intensities of the reflexions obtained from the characteristic curve of the film. These intensities were corrected in the usual way for multiplicity and Lorentz and polarization factors. The correction for absorption was carried according to the absorption-factor tables for a cylindrical specimen.[7] The absorption coefficient, μ, calculated from these tables, was 2030 cm.$^{-1}$.

Fifty-two possible reflexions gave only 38 diffraction lines on the photograph, because of the overlapping of several reflexions having nearly equal Bragg angles. The intensities of the integral reflexions in such cases were evaluated by division of the total observed intensity in the ratio of the calculated intensities. The inaccuracy introduced by such an estimation probably influenced the fluorine parameter only, whereas it should have no significant effect on the mercury parameter.

Determination of the Atomic Parameters.—The mercury and fluorine atoms are located in special positions having symmetry 4 mm, the co-ordinates being 0,0,z; $\frac{1}{2},\frac{1}{2},\frac{1}{2}-z$; 0,0,$z$; $\frac{1}{2},\frac{1}{2},\frac{1}{2}-z$. Consequently only two parameters, z_{Hg} and z_F had to be determined. The preliminary z_{Hg} co-ordinate was obtained by the usual trial-and-error methods and by means of a Patterson

Electron-density distribution along [001] *in the crystal structure of mercurous fluoride*



—●— *Fourier synthesis,* $\rho_o = \rho\ (x, y, z)$ *for* $x = 0$, $y = 0$.
—○— *Difference synthesis,* $\rho_o - \rho_{Hg}$.

The values of the function in e.Å^{-3} *are given at* 1/60 *of the* c*-period.*

line synthesis. The signs of all observed structure factors, $F_o(hkl)$, were computed by neglecting the contributions of the fluorine atom. The three-dimensional electron-density distribution was calculated for the line (0,0,z) in intervals of 1/60 of the c-axis, with Beevers–Lipson strips. The result of the summation is shown in the Figure. The parameters are: $z_{Hg} = 0{\cdot}111$; $z_F = 0{\cdot}322$. The fluorine-atom peak has appeared although influenced by diffraction effects from the mercury atom. The value of z_{Hg} differs only slightly from that obtained by trial-and-error methods. The absolute scale of the structure factors and temperature factor were determined by Wilson's method, and the observed structure factors were corrected accordingly.

To refine the fluorine co-ordinate a difference synthesis with $(F_o - F_{Hg})$ as coefficients was computed. F_{Hg} was calculated by using f_{Hg} values from the "Internationale Tabellen,"[8] multiplied by a temperature factor with $B = 5{\cdot}5$ Å^2. The result is shown in the Figure, together with the F_o synthesis. The slope of $\rho_o - \rho_c$(Hg) is zero at the point $z = z_{Hg}$. The fluorine-atom peak appeared without significant change at $z_F = 0{\cdot}323$.

Observed and calculated structure factors obtained in this way are given in Table 1. The agreement is satisfactory and the reliability index $R = \sum\big||F_o| - |F_c|\big| / \sum|F_o|$ is 0·10.

Accuracy of Atomic Co-ordinates.—Cruickshank's method[9] for the determination of the

[7] "Internationale Tabellen zur Bestimmung der Kristallstrukturen," Borntraeger, Berlin, 1935, Vol. II., p. 583.
[8] *Op. cit.*, p. 571.
[9] Cruickshank, *Acta Cryst.*, 1949, **2**, 65.

standard deviation, $\sigma(z)$, was applied. The result is $\sigma(z) = 0{\cdot}02$ Å for the mercury and 0·03 Å for the fluorine-atom co-ordinate. This gives a standard deviation of 0·04 Å for the Hg–Hg bond length.

Final atomic co-ordinates are for Hg $z = 0{\cdot}111$, and for F $z = 0{\cdot}323$.

TABLE 1. *Observed and calculated values of the structure factors.*

$\sin^2\theta_{obs.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	$\sin^2\theta_{obs.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	$\sin^2\theta_{obs.}$	*hkl*	$F_{obs.}$	$F_{calc.}$
0·049	101	154	181	0·438	310	63	66		400	31	31
0·080	004	246	−205		303	25	−26	0·748	411	16	19
0·088	110	218	229	0·448	109	81	62	0·756	318	22	17
	103	78	83	0·462	312	10	8	0·781	404	21	−22
0·168	114	142	−152	0·466	217	10	8	0·788	330	23	24
	105	157	−166	0·493	208	37	34	0·788	413	9	−10
0·175	200	153	168		0,0,10	48	44	0·798	309	20	23
	006	67	− 74	0·518	314	48	−45	0·806	1,1,12	10	− 9
0·225	121	87	98		305	51	−48	0·853	2,2,10	13	15
0·255	204	106	106	0·574	321	35	31	0·869	334	15	−16
0·263	213	51	− 47	0·587	11,1,0	37	32		415	16	−17
0·288	116	46	− 59	0·624	323	18	−15	0·887	406	9	− 9
0·319	008	60	62		316	20	−17		1,0,13	16	−17
0·343	215	95	− 87		129	42	36	0·938	3,1,10	11	12
0·349	220	78	90	0·672	228	22	20	0·957	424	10	−13
0·398	301	46	54		2,0,10	28	25	0·970	336	7	− 7
0·407	118	56	47	0·695	325	30	−29	0·980	0,0,14	13	−13
0·429	224	51	− 59								

DISCUSSION

From the above parameters the Hg–Hg bond length in mercurous fluoride is 2·43 ± 0·05 Å, and as can be seen from Table 2, this fits well into the series of Hg–Hg bond length values for mercurous halides.

TABLE 2. *Comparison of the* Hg–Hg *bond lengths in mercurous halides* (*in* Å).

Hg_2F_2	2·43 ± 0·04	Present authors
Hg_2Cl_2	2·53	Havighurst [2]
Hg_2Br_2	2·58	,,
Hg_2I_2	2·69	,,

It is certain that the degree of ionic character of the mercury–halogen bond decreases from fluoride to iodide, and this can be roughly estimated from the differences in the corresponding electronegativities.[10] It seems therefore that the bond length in mercurous halides is related to the electronegativity of the halogen. It may be concluded that, in spite of the positive charge on both mercury atoms, the mercurous ion is relatively more stable than a covalently bonded mercurous group. This conclusion is supported by the fact that it has so far proved impossible to prepare organic mercurous compounds. The only problem is whether the mercurous ion can occur as a free ion at all, since, as shown in the preceding paper, the mercurous ion in the crystal of $Hg_2(NO_3)_2.2H_2O$ is co-ordinated with water molecules, and it is very likely that this co-ordination persists in aqueous solutions. A simplified model may be suggested in which the structure of mercurous fluoride is explained in terms of mercurous Hg–Hg^{2+} and F^- ions, and the structure of mercurous iodide in terms of dimerized HgI radicals. Mercurous chloride and bromide can be considered as intermediate in character. Nevertheless still more data on the properties of mercurous compounds are necessary before the nature of bonds in these compounds can be fully understood.

The Hg–F distance, 2·31 Å, is smaller than the sum of the corresponding ionic radii (Hg 1·10 Å, F 1·36 Å), and is larger than the sum of the covalent radii (Hg 1·48, F 0·72 Å), the value for the radii being taken from Wells's book.[11] The remarkably large fluorine–fluorine distance in the [001] direction should be mentioned. It is 3·85 Å and shows that here, in contrast to the other mercurous halide structures, there is no contact between the halogen atoms in this direction. This is presumably due to the small ionic radius of fluorine

[10] Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1940, p. 41.
[11] Wells, "Structural Inorganic Chemistry, 2nd Edn., Oxford, 1950, pp. 50, 58, 70.

compared with that of chlorine, which changes the packing conditions very markedly in passing from mercurous chloride to the fluoride. It is interesting that this change is shown only in a shortening of the *a* dimension (from 4·47 Å for calomel to 3·66 Å for mercurous fluoride) while the *c* dimension remains practically the same (10·89 Å for calomel and 10·90 Å for mercurous fluoride). In consequence there is a close approach of 2·70 Å between the mercury and the fluorine atom of neighbouring molecules and this prevents a closer approach in the [001] direction.

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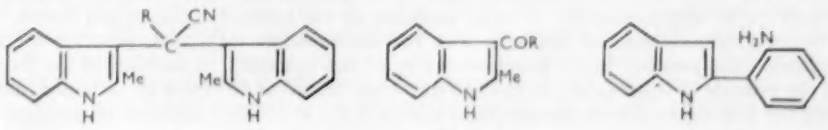
268. *The Action of Acyl Cyanides on 2- and 1 : 2-Substituted Indoles. Part II.* Derivatives of 2-o-Aminophenylindole.*

By A. K. Kiang, F. G. Mann, A. F. Prior, and A. Topham.

Acetyl cyanide reacts with 2-*o*-aminophenylindole to give the acetamido-indole, 2-methylindolo(3′ : 2′-3 : 4)quinoline, and the isomeric 2-methylindolo-(1′ : 2′-3 : 4)quinazoline under various conditions. Benzoyl cyanide similarly gives the benzamido-indole and the 2-phenylindoloquinoline. The inter-relation of these compounds is discussed.

Acetyl and benzoyl cyanides with 2-*o*-aminophenyl-1-methylindole give the corresponding acylamino-indoles and indoloquinolines.

In Part I,* Kiang and Mann have shown that 2-methylindole in pure chloroform solution reacted with acetyl cyanide to give 1-cyano-1 : 1-di-(2-methyl-3-indolyl)ethane (I; R = Me) and a smaller proportion of 3-acetyl-2-methylindole (II; R = Me): in chloroform containing a small quantity of hydrogen chloride only the cyano-ethane was formed, whereas in chloroform containing a trace of pyridine the acetyl-indole was the sole product. Benzoyl cyanide reacted similarly with 2-methylindole in chloroform containing hydrogen chloride to give the nitrile (I; R = Ph), and in chloroform with a trace of pyridine to give 3-benzoyl-2-methylindole (II; R = Ph). It is noteworthy that although the action of



(I) (II) (III)

acetyl and benzoyl cyanide on several other 2- and 1 : 2-substituted indoles was investigated, no other examples of simple acylation in the 3-indole position in neutral or acid solution were encountered, the product being usually a di-indolyl compound analogous to (I): furthermore, a 2-substituted indole was never attacked in the 1-position.

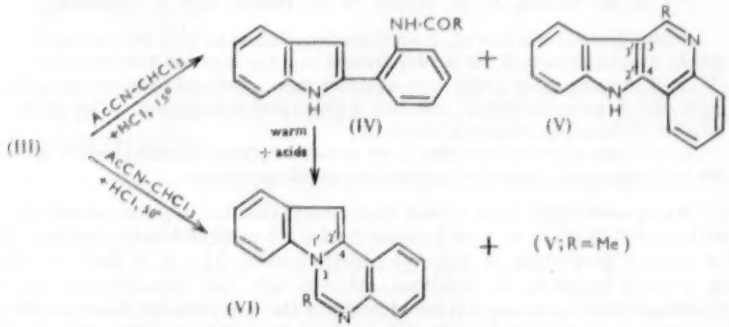
Having thus elucidated the reactions of these simpler indoles, we have now investigated the action of the two acyl cyanides on 2-*o*-aminophenylindole (III): a greater variety of reactions is now possible, since this indole has three potential points of attack, namely, the amino-group and the 1- and the 3-position in the indole nucleus.

We find that 2-*o*-aminophenylindole (III) and acetyl cyanide (2 equivalents) in chloroform solution interact, slowly at room temperature and readily on boiling, to give 2-*o*-acetamidophenylindole (IV; R = Me). Mildly acidic conditions, *i.e.*, when the above

* Part I, *J.*, 1953, 594.

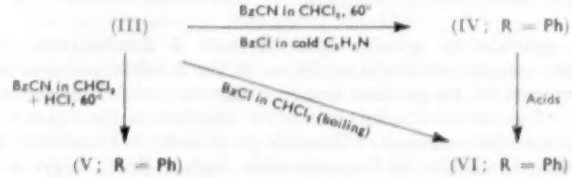
solution is treated at room temperature with chloroform saturated with hydrogen chloride, produce a mixture of the acetamido-compound (IV; R = Me) and the hydrochloride of 2-methylindolo(3′ : 2′-3 : 4)quinoline (V; R = Me), the latter being identical with a sample prepared by the method of Kermack and Smith.[1] More vigorous conditions, *i.e.*, when hydrogen chloride was passed through the above solution at 50°, produce a mixture of the hydrochlorides of the above quinoline (V; R = Me) and of the isomeric 2-methylindolo-(1′ : 2′-3 : 4)quinazoline (VI; R = Me). These conditions are those of the Hoesch reaction, and the addition of stannic or aluminium chloride to the solution had little effect on the products.

Now it is significant that the acetamido-compound (IV; R = Me), which can be prepared by the cautious acetylation of the indole (III), is very sensitive to acids, which readily cyclise it solely to the corresponding salt of the quinazoline (VI; R = Me): this process occurs when the compound (IV; R = Me) is dissolved in cold concentrated hydrochloric acid, or when it is briefly heated with dilute hydrochloric acid, or with acetic acid containing hydrogen chloride, or with ethanol containing a very low concentration of hydrogen chloride. Moreover, the indole (III) with cold acetyl chloride or bromide or warm acetic anhydride gives the quinazoline (VI; R = Me). In none of these experiments could the quinoline (V; R = Me) be detected as a product of the cyclisation of the acetamido-indole (IV; R = Me).



The formamido-compound (IV; R = H) must be particularly sensitive to acids, since all attempts to obtain it by formylation of the indole (III) gave indolo(1′ : 2′-3 : 4)quinazoline (VI; R = H), which was identified by its marked difference from the authentic indolo(3′ : 2′-3 : 4)quinoline (V; R = H) prepared by the method of Clemo and Perkin.[2]

Benzoyl cyanide reacted similarly with the amino-indole (III) with however certain differences, due possibly to the lower reactivity of this cyanide. A solution of the indole and the cyanide (2 equivalents) in chloroform, when heated at 60° for 4 hr. or boiled under reflux for 1 hr., gave 2-*o*-benzamidophenylindole (IV; R = Ph); addition of pyridine to



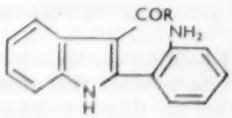
the boiling chloroform solution did not alter the result. The benzamido-derivative could also be obtained by direct benzoylation, for example, by the addition of benzoyl chloride to a pyridine solution of the indole (III). When however a stream of hydrogen chloride

[1] Kermack and Smith, *J.*, 1930, 2000.
[2] Clemo and Perkin, *J.*, 1924, **125**, 1608.

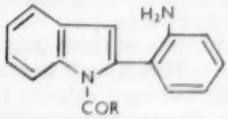
was passed into the original chloroform solution at 60° for 4 hr., only the hydrochloride of 2-phenylindolo(2′ : 3′-4 : 3)quinoline (V; R = Ph) was obtained: this base was identified by an independent synthesis. Under the above conditions, the formation of the isomeric quinazoline (VI; R = Ph) was not observed. The benzamido-compound (IV; R = Ph) is however also very sensitive to acids which readily convert it into the quinazoline: similarly the indole (III) with benzoyl chloride in boiling chloroform gives the quinazoline (VI; R = Ph), undoubtedly *via* the compound (IV; R = Ph).

It is highly significant therefore that in both the acetyl and the benzoyl series, the acid-catalysed cyclisation of the acylamino-compound (IV) gave solely the quinazoline (VI), and that the quinoline (V) could not be thus prepared: consequently the formation of the latter from the indole (III) must proceed through some intermediate other than the acylamino-compound (IV). The structure of the acylamino-compounds experimentally obtained is therefore of considerable importance, for the acyl derivative (IV) should theoretically be capable of cyclisation to either the quinoline (V) or the quinazoline (VI), whereas the 3-acyl isomer (VII) could give only the quinoline (VI), and the 1-acyl isomer (VIII) only the quinazoline (VI).

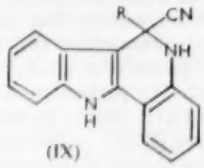
The acetamido-compound (IV; R = Me), prepared on many occasions, was always obtained as a highly crystalline compound, m. p. 156—157°: its cold ethanolic solution gave an immediate deep colour with Ehrlich's reagent, indicating strongly that the 1- and the 3-position in the indole were unsubstituted. The benzamido-compound, prepared from the cyanide or by direct benzoylation, was also a crystalline compound, m. p. 176°. On one occasion, a small portion of the indole (III), when benzoylated by the Schotten–Baumann method, gave an isomeric benzamido-derivative, m. p. 167°, depressed to 142—147° on admixture with the former compound. Although the preparation of the product,



(VII)



(VIII)



(IX)

m. p. 167°, was once repeated independently by another worker, further attempted repetitions, using the same sample of the indole (III) and many other samples, and a wide variety of conditions, always gave the original product, m. p. 176°.* It is almost certain that the latter has the structure (IV; R = Ph), for its cold ethanolic solution rapidly gave a deep colour with Ehrlich's reagent, whereas that of the isomer, m. p. 167°, gave no colour. Neither compound in ethanolic solution gave a precipitate with 2 : 4-dinitrophenylhydrazine, and it is probable therefore that the isomer, m. p. 167°, has the structure (VIII; R = Ph), a conclusion supported by the cyclisation of the minute quantity available (p. 1325).

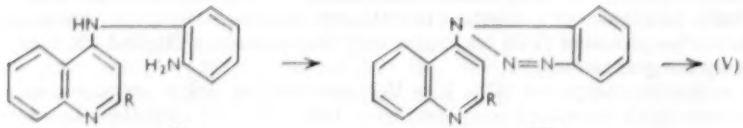
The precursor of the indoloquinolines (V) remains uncertain. Since the latter were formed in the most acidic medium, it is possible that the amino-group in the indole (III) was inactivated by hydrochloride formation, and the acyl cyanide then gave the 3-acyl derivative (VII), with subsequent cyclisation to the quinoline (V). This is unlikely, however, because acyl cyanides react with simpler indoles to give 3-acyl derivatives in good yield only in basic media (cf. Part I). The precursor may be the compound (IX), which

* This failure to repeat the preparation of an acylated indole is not without precedent. The preparation of 3 : 6-dibenzoylcarbazole from 9-benzoylcarbazole by Plant and Tomlinson [3] could not be repeated by Plant, Rogers, and Williams,[4] who state "These discordant observations have not been traced to any obvious variations in conditions and are probably due to very minor changes in the quality of the materials used." The conversion of 2 : 3-diphenylindole into its 1-benzoyl derivative by Fennell and Plant [5] could not be subsequently repeated (personal communication from the late Dr. S. G. P. Plant).

[3] Plant and Tomlinson, *J.*, 1932, 2188.
[4] Plant, Rogers, and Williams, *J.*, 1935, 742.
[5] Fennell and Plant, *J.*, 1932, 2872.

could be formed in a reaction the speed of which is dependent on the acidity of the medium, which would therefore determine the relative proportions of the compound (IX) and the acylamino-compound (IV); this precursor under the influence of the hydrogen chloride could readily undergo aromatisation by loss of hydrogen cyanide, giving the stable hydrochloride of the indoloquinoline (V).

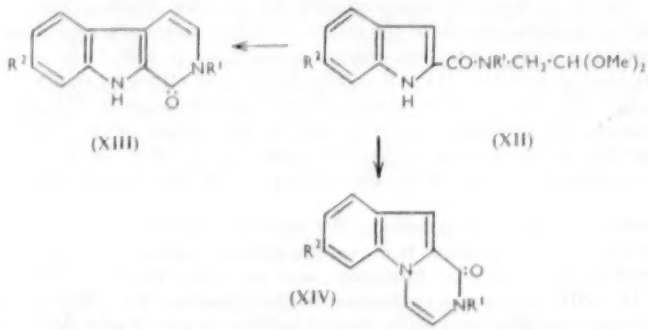
The indoloquinazolines (VI; R = H, Me, and Ph) represent a new heterocyclic system, the structure of which follows from their non-identity with the isomeric indoloquinolines (V; R = H, Me, and Ph). The first two of the latter compounds had previously been synthesised, and the third (V; R = Ph) has now been prepared by a method based essentially on the work of Robinson and Thorneley [6] (cf. also Holt and Petrow [7]). 4-Chloro-2-phenylquinoline was condensed with *o*-phenylenediamine to give 4-*o*-aminoanilino-2-phenylquinoline (X; R = Ph) which with nitrous acid furnished 4-1′-benzotri-



azolyl-2-phenylquinoline (XI; R = Ph). This compound, when heated with phosphoric acid, lost nitrogen with cyclisation to the required 2-phenylindolo(2′ : 3′-4 : 3)quinoline (V; R = Ph). The 2-benzyl analogue (V; R = CH_2Ph) has been similarly synthesised to distinguish it from the 2-benzylindoloquinazoline (VI; R = CH_2Ph) obtained by cyclisation of the phenylacetamido-indole (IV; R = CH_2Ph).

It is noteworthy that salts of these indoloquinolines (V) are colourless, whilst those of the indoloquinazolines (VI) are bright yellow.

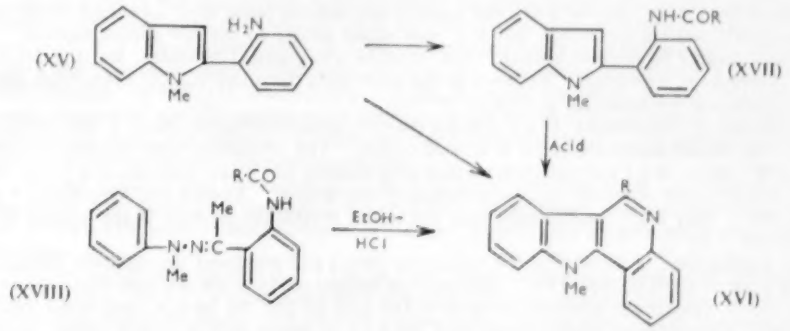
Cyclisation of a 2-substituted indole to the 3- and the 1-position has been previously recorded. In particular, Kermack, Perkin, and Robinson [8] have shown that compounds of type (XII) cyclise in ethanolic hydrogen chloride to either the dihydroindolopyridine derivative (XIII) or the isomeric dihydroindolopyrazine derivative (XIV) or a mixture of both, the nature of the products depending on the substituents R^1 and R^2.



We have also investigated the simpler problem of the action of acetyl and benzoyl cyanides on 2-*o*-aminophenyl-1-methylindole (XV), where cyclisation can now give only the indoloquinolines (XVI). In this series also, there are certain differences in the action of the two acyl cyanides. The methylindole (XV) reacts with acetyl cyanide in a basic medium, *i.e.*, in pyridine or in chloroform containing pyridine, to give the acetamido-derivative (XVII; R = Me), but in neutral and acidic media, *i.e.*, in pure chloroform and in chloroform

[6] Robinson and Thorneley, *J.*, 1924, 2169.
[7] Holt and Petrow, *J.*, 1948, 922.
[8] Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1872.

containing hydrogen chloride respectively, to give the indolo-quinoline (XVI; R = Me), the reaction being most rapid in the acidic medium. The indole (XV) reacts with benzoyl cyanide in both the above basic and neutral media to give the benzamido-derivative (XVII; R = Ph), and in chloroform containing hydrogen chloride to give the quinoline (XVI;



R = Ph). The acylamino-compounds (XVII) are again very sensitive to acids, which readily cyclise them to the indoloquinolines (XVI): it is noteworthy that in this series the formamido-compound (XVII; R = H) can be isolated, unlike the unmethylated analogue (IV; R = H). The identity of the indoloquinolines (XVI; R = Me and Ph) has been confirmed by their formation by cyclisation of the appropriate *o*-acylaminoacetophenone methylphenylhydrazone (XVIII): this reaction was originally performed by Kermack and Smith,[1] but the yield and quality of the final product are much improved if ethanolic hydrogen chloride is used as a condensing agent in place of phosphorus oxychloride.

Infrared data for various indoles are given on p. 1330.

Experimental

The indole (III), its acyl derivatives, and the indoloquinazolines obtained by their cyclisation are described first, then (when necessary) the synthesis of the indoloquinolines, so that the members of these three classes are identified before describing their production by the action of acyl cyanides on the indole. The indole (XV) is then similarly treated, although the quinazoline compounds do not occur in this series.

2-*o*-*Aminophenylindole* (III).—(a) *o-Nitrobenzoyl chloride.* Powdered phosphorus pentachloride (138 g.) was gradually added with shaking to *o*-nitrobenzoic acid (102 g.) in a 1 l. flask fitted with a reflux condenser closed with a calcium chloride tube, and the mixture was heated for 20 min. on a boiling-water bath. Phosphorus oxychloride was removed by distillation (water-pump), and the residual oily *o*-nitrobenzoyl chloride, which cannot always be safely distilled, was then filtered through a sintered glass funnel (yield, 108 g., 95%). It was sufficiently pure for the next stage.

(b) *o-Nitroacetophenone.* Two solutions were prepared: solution A by dissolving sodium wire (27·8 g.) in absolute ethanol (450 c.c.), which was cooled and restored to 440 c.c. with more ethanol, and solution B by dissolving the above chloride (73 c.c., 100 g.) in ether, the solution being then made up to 100 c.c.

Ethyl malonate (103 c.c.) was placed in a 1 l. flask, cooled in ice–salt. Solutions A and B were slowly added through two funnels in the following order so that the temperature of the mixture did not rise above 5°: A 240 c.c., B 50 c.c., A 100 c.c., B 25 c.c., A 50 c.c., B 15 c.c., A 50 c.c., B 10 c.c. After 10 min., the mixture was added to a solution of concentrated sulphuric acid (25 c.c.) in water (500 c.c.). The precipitated oil was extracted with ether, which was then thoroughly shaken with water. The initial solution, combined with the water-washings, was again extracted with ether, which was then washed with water. The united ether extracts were distilled, and traces of solvent removed from the residual ethyl *o*-nitrobenzoylmalonate on a water-bath at 15 mm. until distillation ceased. The residue was mixed with a solution of sulphuric acid (270 c.c.) in water (925 c.c.), boiled under reflux for 4 hr., cooled, and extracted

with ether. The extract was washed in turn with an excess of aqueous 10% sodium hydroxide and with water, and the solvent removed, and the residue, after heating at 100°/15 mm., consisted of almost pure *o*-nitroacetophenone (74 g., 83%). This method is less troublesome and gives higher yields than any of those described by Schofield and Swain.[9]

(c) *o-Aminoacetophenone.* A mixture of *o*-nitroacetophenone (68 g.) and concentrated hydrochloric acid (380 c.c.) was treated at 95° under reflux, with vigorous stirring, with granulated tin (153 g.) during 1 hr., the heating and stirring being then continued for 30 min. Aqueous 30% sodium hydroxide (470 c.c.) was added slowly to the hot stirred mixture, with occasional cooling to prevent boiling. The mixture was distilled in steam, and the distillate (*ca.* 4 l.) extracted with ether. Removal of the ether from the dried (K_2CO_3) extract left almost pure *o*-aminoacetophenone (42 g., 73%).

A mixture of this product (43 g.), ethanol (84 c.c.), phenylhydrazine (35 c.c.), and acetic acid (5 c.c.) was boiled under reflux for 6 hr. and cooled. The crystalline phenylhydrazone (m. p. 104—108°; 63 g., 88%) was collected, washed with ethanol, and dried, a second crop (m. p. 103—108°; 3·5 g.) being obtained by concentration of the filtrate. Auwers and Meyenburg [10] give m. p. 108°: they state inaccurately that the initial crystalline product is the acetate of the hydrazone.

(d) *Cyclisation.* A mixture of the hydrazone (50 g.) and powdered zinc chloride (250 g.) was stirred in an oil-bath at 160—170°. The mixture became pasty as the internal temperature rose to *ca.* 210°. The stirred mixture was kept in the bath at 160° for 10 min., and when removed solidified. Concentrated hydrochloric acid (43 c.c.) in water (615 c.c.) was added, and the stirred mixture heated on the water-bath for *ca.* 1 hr. until the zinc chloride had been extracted. The mixture, after further dilution with water (440 c.c.) and hydrochloric acid (44 c.c.), was heated to boiling to obtain an almost clear solution, to which ammonia (17%; *ca.* 87 c.c.) was slowly added until the mixture was no longer acid to Congo-red. The precipitate was collected, washed with water, and dissolved in boiling water (1060 c.c.) containing hydrochloric acid (88·5 c.c.), and the filtered solution treated with ammonia (*ca.* 126 c.c.) as before. The precipitated indole (III), when washed and dried (38·5 g., 84%), had m. p. 148—150°, increased to 154—156° by recrystallisation from ethanol, and then unchanged by sublimation at 145°/0·001 mm. (Found: C, 80·6; H, 5·9. Calc. for $C_{14}H_{12}N_2$: C, 80·7; H, 5·8%) (lit.,[11] m. p. 154°). The use of a lower proportion of zinc chloride reduced the yield: the use of ethanolic hydrogen chloride as a cyclising agent gave very poor results.

Acyl Derivatives of the Indole (III).—(1) 2-*o*-*Acetamidophenylindole* (IV; R = Me). When the powdered indole (III) (3 g.) was added to cold acetic anhydride (6 c.c.), heat was evolved, giving a clear solution which when set aside for 1 hr. deposited crystals of the acetamido-derivative (IV; R = Me). After ice-water cooling, the product (2·75 g., 75%) was collected and washed with ethanol: it had m. p. 155—156·5°, increased to 156—157° by crystallisation from ethanol (Found: C, 77·15; H, 6·0; N, 11·3. Calc. for $C_{16}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2%). Ruggli and Dinger [12] give m. p. 151—152°. If this preparation is carried out on a larger scale without strong cooling, the higher temperature attained may cause the product to be contaminated with the quinazoline (VI; R = Me).

(2) *Benzamido-derivative* (IV; R = Ph). (*A*) (i) Benzoyl chloride (0·6 c.c., 1·1 mols.) was added to a solution of the indole (1·04 g.) in pyridine (2 c.c.), which was then heated to 50°, set aside for 30 min., and poured into water. The aqueous solution was decanted from the precipitated oil which when stirred with ethanol solidified (1·1 g., 71%), and on crystallisation from ethanol afforded the *benzamido-compound*, needles, m. p. 175—175·5° (Found: C, 80·5; H, 5·0; N, 9·0. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·15; N, 9·0%).

(ii) In numerous attempts to repeat the preparation of the isomer described below in (*B*), the general conditions were varied widely without effect. The powdered indole, when stirred with cold undiluted chloride, was converted into the hydrochloride of the indoloquinazoline (VI; R = Ph).

(*B*) On two occasions a suspension of the pure powdered indole in an excess of 10% aqueous sodium hydroxide, when shaken with a small excess of benzoyl chloride, rapidly gave a pale brown emulsion which slowly solidified. The solid product, recrystallised from ethanol, gave cream-coloured crystals of the benzamido-compound, m. p. 166°, depressed to 148—160° on admixture with the previous compound (Found: C, 80·5; H, 4·9%).

[9] Schofield and Swain, *J.*, 1948, 384.
[10] Auwers and Meyenburg, *Ber.*, 1891, **24**, 2370.
[11] Kliegl and Haas, *Ber.*, 1911, **44**, 1211.
[12] Ruggli and Dinger, *Helv. Chim. Acta*, 1939, **22**, 908.

(3) *Phenylacetamido-derivative* (IV; R = CH_2Ph). Phenylacetyl chloride (1·32 c.c., 1 mol.), when added dropwise to a solution of the indole (III) (2·0 g.) in pyridine (2 c.c.), caused a vigorous reaction, and the oily product, when set aside for 15 min. and then stirred with *cyclo*hexane, deposited the *phenylacetamido-derivative* (1·2 g., 41%), m. p. 169—170° after crystallisation from ethanol (Found: C, 80·7; H, 5·7. $C_{22}H_{18}ON_2$ requires C, 80·9; H, 5·6%).

Cyclisation to Indolo(1′ : 2′-3 : 4)*quinazolines* (*Ring Index*, *Indolo*[1 : 2-c]*quinazolines*) (VI).—(1) A solution of the indole (III) (1 g.) in chilled formic acid (10 c.c.) was evaporated at room temperature over sodium hydroxide in a vacuum-desiccator. The dry crystalline residue of *indolo*(1′ : 2′-3 : 4)*quinazoline* (VI; R = H), when washed with cold ethanol and dried, had m. p. 198—200°; recrystallisation from ethanol gave very pale yellow crystals (0·9 g.), m. p. 200—201° (Found: C, 82·7; H, 4·8; N, 12·8. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·8%). The same compound was obtained when a solution of the indole (1 g.) in formic acid (5 c.c.) or in formamide (4 c.c.) was boiled for 10 min. and then poured into water. The indole was unaffected when its solution in ethyl formate was boiled.

(2) (*a*) A solution of the indole (III) (2 g.) in acetic anhydride (10 c.c.), when boiled under reflux for 2 hr. and cooled, furnished the crystalline 2-methylindoloquinazoline (VI; R = Me), m. p. 114—116° after crystallisation from ethanol, undepressed by admixture with the product (*b*) below.

When acetyl chloride (0·5 c.c., 1·5 mols.) was slowly added to a solution of the indole (1 g.) in chloroform (20 c.c.) a violent reaction occurred, and the yellow hydrochloride of the indoloquinazoline was deposited. This salt (1·4 g.) was collected and dissolved in hot water (150 c.c.) containing hydrochloric acid (5 c.c.): basification of the solution with ammonia deposited the methylindoloquinazoline (0·84 g.), m. p. 112—114°.

(*b*) A solution of the acetamido-compound (IV; R = Me) (1 g.) in acetic acid (20 c.c.) containing concentrated hydrochloric acid (5 c.c.) was boiled under reflux for 2 hr. and then evaporated to dryness on a water-bath. The residual yellow crystalline hydrochloride, when treated as above, gave the 2-*methylindoloquinazoline* (0·88 g.), pale yellow needles, m. p. 115—116° (from ethanol) (Found: C, 82·2; H, 5·35; N, 12·45. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%).

The acetamido-derivative was also readily converted into the above hydrochloride when its solution in chloroform–hydrogen chloride or in ethanolic hydrogen chloride was gently heated, or when its suspension in an excess of dilute hydrochloric acid was boiled until complete solution was obtained.

(3) (*a*) Solutions of the indole (III) (2·1 g.) and benzoyl chloride (1·15 c.c., 1·1 mols.) each in chloroform (30 c.c. and 10 c.c.) were mixed, boiled under reflux for 3 hr. and evaporated to dryness. The product was extracted with boiling water (500 c.c.) containing 2N-hydrochloric acid (10 c.c.), and the undissolved 2-*phenylindoloquinazoline* (VI; R = Ph) (2·7 g., 92%) had m. p. 194—196°, increased to 197—198° by recrystallisation from ethanol (Found: C, 85·75; H, 4·6; N, 9·7. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·75; N, 9·5%). Alternatively, when hydrogen chloride was passed through the above mixture at 60° for 3 hr., the product, worked up as before, furnished the indoloquinazoline (1·23 g.), m. p. 197—198°.

(*b*) A solution of the benzamido-derivative (IV; R = Ph), m. p. 175—175·5° (0·1 g.), in chloroform (5 c.c.) containing ethanolic hydrogen chloride (0·1 c.c.) was boiled for 3 hr. and evaporated. The yellow residue of crude hydrochloride (m. p. 140—194°), on recrystallisation as before, underwent dissociation giving the indoloquinazoline, m. p. and mixed m. p. 195—197°.

The isomeric benzamido-compound, m. p. 166—167° (*ca.* 2 mg.), was boiled with ethanolic hydrogen chloride for 10 min., the solution immediately developing a bright yellow colour. Evaporation gave a residue which on basification with ammonia furnished the crudec yclised product, m. p. 188—192°, insufficient in quantity for recrystallisation or mixed m. p. determination. The deep yellow colour of the hydrochloride, and the m. p. of the product, indicate strongly that this product was also the indoloquinazoline (VI; R = Ph) and that this benzamido-compound has therefore the structure (VIII).

(4) (*a*) Phenylacetyl chloride (1·33 c.c.) was added to a hot solution of the indole (III) (2·1 g.) in chloroform (40 c.c.), which was boiled under reflux for 75 min. and cooled. The yellow crystals (m. p. *ca.* 254°; 2·4 g.) of the hydrochloride which had separated were collected, and when crystallised from ethanol gave the almost colourless 2-*benzylindoloquinazoline* (VI; R = CH_2Ph), m. p. 194—197° (Found: C, 85·65; H, 5·0; N, 8·95. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%).

(*b*) A solution of the phenylacetamido-compound (IV; R = CH_2Ph) in chloroform, treated as in 3(*b*), gave the quinazoline, m. p. and mixed m. p. 195—198·5°.

2-*Phenylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = Ph).—(*a*) 4-Hydroxy-2-phenylquinoline was prepared by the condensation of ethyl anthranilate and acetophenone diethyl acetal[13] and converted into 4-chloro-2-phenylquinoline essentially by the method of Knorr and Fertig.[14] A mixture of the chloro-compound (2·4 g.), *o*-phenylenediamine (1·1 g., 1 mol.), copper powder (0·05 g.), and concentrated hydrochloric acid (0·1 c.c.) was heated at 18 mm. Reaction started when the bath-temperature reached *ca.* 120° and became very vigorous at 130° : the temperature was kept at 130° until the reaction appeared to cease, and was then increased to 140° for 5 min. The cold product was extracted with boiling ethanol (200 c.c.), which was filtered into an excess of dilute ammonia. The greenish precipitate was washed with water, dried (2·85 g.), and extracted with boiling benzene. The filtered extract on cooling deposited a powder, m. p. 178—180°, which, recrystallised from ethanol, gave the hydrated 4-*o*-*aminoanilino*-2-*phenylquinoline* (X; R = Ph), as very pale yellow crystals, m. p. 179—181° (Found : C, 77·9; H, 6·5; N, 12·8. $C_{21}H_{17}N_3,0{\cdot}75H_2O$ requires C, 77·7; H, 5·7; N, 12·9%).

(*b*) An ethanolic solution of the amino-compound (X; R = Ph) was mixed with N-hydrochloric acid, cooled to 5—10° with stirring, and treated with a slight excess of sodium nitrite. The crystals which separated were collected and recrystallised from methanol, affording colourless 4-1′-*benzotriazolyl*-2-*phenylquinoline* (XI; R = Ph), m. p. 152—153° (Found : C, 78·3; H, 4·5; N, 17·6. $C_{21}H_{14}N_4$ requires C, 78·2; H, 4·4; N, 17·4%). A solution in hot 10% hydrochloric acid on cooling deposited the crystalline *monohydrochloride*, m. p. 185—186° (Found : C, 70·2; H, 4·6; N, 15·8. $C_{21}H_{14}N_4,HCl$ requires C, 70·3; H, 4·2; N, 15·6%).

(*c*) The triazole (1 g.) was heated in syrupy phosphoric acid (10 c.c.) at 140—150° until evolution of nitrogen ceased and then at 150° for 1 min. The product was poured into ice-water containing sodium hydroxide (8 g.), and the precipitate washed with water, dried (0·85 g.), and extracted with boiling benzene. The filtered extract was evaporated and the residue, when recrystallised from benzene, afforded 2-*phenylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = Ph), m. p. 245—246°. This still contained an impurity, for in concentrated sulphuric acid it gave a colourless solution with a blue fluorescence. This impurity could not be removed by absorption on an alumina column : the base was therefore converted into its hydrochloride, which was repeatedly recrystallised from dilute hydrochloric acid, in which the impurity was only slightly soluble. The regenerated base, of unchanged m. p., no longer gave a fluorescent solution (Found : C, 86·0; H, 5·1; N, 9·3. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·75; N, 9·5%).

A filtered solution of the base (0·5 g.) in hot water (50 c.c.) containing concentrated hydrochloric acid (0·5 c.c.), when allowed to cool, initially formed a gel, which, when drained as far as possible at the pump and then repeatedly recrystallised, gave the *monohydrated monohydrochloride*, m. p. 326—344° (Found : C, 72·0; H, 5·2; N, 8·15; Cl, 10·25. $C_{21}H_{14}N_2,HCl,H_2O$ requires C, 72·2; H, 4·9; N, 8·1; Cl, 10·2%).

2-*Benzylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = CH_2Ph).—(*a*) *Ethyl* α-(*phenylacetyl*)*acetoacetate and* γ-*phenylacetoacetate*. A buffered copper sulphate solution was prepared by mixing aqueous solutions of hydrated copper sulphate (22·8%; 1650 c.c.), sodium formate (40%; 765 c.c.), and formic acid (85%; 81 c.c.).

Ethyl acetoacetate (127 c.c.) was added to a solution of sodium (23 g.) in absolute ethanol (372 c.c.), which was then stirred at 0—5° during the slow addition in turn of (i) phenylacetyl chloride (53 c.c.), (ii) a solution of sodium (9·2 g.) in ethanol (150 c.c.), and (iii) the chloride (32 c.c.). The mixture was added with stirring to concentrated hydrochloric acid (76 c.c.), diluted with water (500 c.c.), then made just alkaline to Congo-red with 30% aqueous sodium hydroxide (*ca.* 12 c.c.). The above copper sulphate solution (600 c.c.) was then added, and after 15 min. the blue copper derivative of ethyl α-(phenylacetyl)acetoacetate was collected, shaken with 95% ethanol (300 c.c.) for 5 min., again collected, washed with ethanol, and dried : the complex (130 g.) had m. p. 177—178° (lit.,[15] m. p. 182—183°).

A mixture of this complex (134 g.), ether (400 c.c.), hydrochloric acid (60 c.c.), and crushed ice was stirred at 0—5° for several hours until a clear solution was obtained. The ethereal layer was washed in turn with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, and then dried and distilled to remove solvent; final heating under reduced pressure left the residual ester (115·5 g.) as a pale brown oil, pure enough for the next stage.

This ester (107 c.c.) was added to a 0·85N-ethanolic ammonia (832 c.c.), from which next day the excess of ammonia and ethanol were removed at 50°/15 mm. A solution of the residue in

[13] Fuson and Burness, *J. Amer. Chem. Soc.*, 1946, **68**, 1270.
[14] Knorr and Fertig, *Ber.*, 1897, **40**, 938.
[15] Bülow and Hailer, *Ber.*, 1902, **35**, 929.

methanol (1170 c.c.), chilled in ice-water, was treated with a 2·5% solution of copper acetate in 50% aqueous methanol (1760 c.c.). The precipitated copper complex of ethyl γ-phenylacetoacetate (60 g.), when washed with methanol (200 c.c.) and dried, had m. p. 125—125·5°. Zangg [16] gives m. p. 128—129°.

A mixture of the complex (69·5 g.), 2N-hydrochloric acid (175 c.c.), and ether (200 c.c.) was shaken until clear, and the ethereal layer washed in turn with the acid and with water, and dried. Removal of the ether, finally under reduced pressure, gave the residual ethyl γ-phenylacetoacetate as a colourless oil (59·5 g.).

Close adherence to the above conditions is necessary for the successful preparation of the esters, particularly the latter. The conditions recorded in the literature gave unsatisfactory results.

(*b*) A mixture of the above ester (20·6 g.), aniline (10 c.c.), benzene (25 c.c.), and acetic acid (0·25 c.c.) was heated under reflux at 125° for 4 hr., water being removed meanwhile through a still-head. The benzene was then removed, finally at 95°/15 mm., and the residual ethyl β-anilino-γ-phenylcrotonate, after recrystallisation from methanol, had m. p. 95—95·5° (22·2 g.) (lit.,[17] m. p. 96—98·5°).

(*c*) The crotonate (30 g.) was added during 2 min. to "Dowtherm" (diphenyl ether 74%, diphenyl 26%) (75 c.c.) at 240°. The mixture was then boiled under reflux for 10 min., cooled, and diluted with light petroleum (b. p. 60—80°) (100 c.c.). The precipitated *2-benzyl-4-hydroxyquinoline* (25·5 g.), when collected, washed with petroleum and dried, had m. p. 209—210°, increased to 210° by recrystallisation from butan-1-ol (Found: C, 82·05; H, 5·6; N, 6·3. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

A mixture of this quinoline (29·5 g.) and phosphorus oxychloride (59 c.c.) was heated at 100° until clear, and the excess of chloride removed under reduced pressure. The cold residue was treated with ice and an excess of aqueous sodium hydroxide, and then extracted with ether. The extract, when washed with water, dried, and evaporated, gave crystalline *2-benzyl-4-chloroquinoline*, m. p. 49—51° (Found: C, 75·5; H, 4·7. $C_{16}H_{12}NCl$ requires C, 75·7; H, 4·7%).

(*d*) A mixture of the chloroquinoline (5 g.) and *o*-phenylenediamine (5 g.) was heated at 140°/25 mm. for 3 hr. The resulting solid *hydrochloride* of 4-*o*-aminoanilino-2-benzylquinoline (X; R = CH_2Ph) was digested with boiling N-hydrochloric acid (100 c.c.), cooled, collected, washed in turn with water and much ethanol, and dried (5·2 g.). Recrystallised from 50% aqueous acetic acid, it had m. p. *ca.* 350° (Found: C, 72·4; H, 5·65; N, 11·5. $C_{22}H_{19}N_3$,HCl requires C, 73·0; H, 5·5; N, 11·6%).

(*e*) A 25% aqueous sodium nitrite solution (5 c.c.) was slowly added to the hydrochloride (6·5 g.) in 2N-hydrochloric (65 c.c.) and acetic acid (65 c.c.) at 0—5°. The solution, evaporated under reduced pressure, gave a gum which was shaken with chloroform and dilute aqueous sodium hydroxide. The chloroform extract, when washed with water, dried, and evaporated, gave the triazole (XI; R = CH_2Ph) as a gum. This was heated with phosphoric acid (*d* 1·75; 65 c.c.) at 170° for 10 min., cooled, and added with stirring to a mixture of 30% aqueous sodium hydroxide (215 c.c.), water (700 c.c.), and chloroform (100 c.c.); the whole was stirred for 2 hr. and then filtered. The chloroform layer, when washed with water, dried, and evaporated, gave *2-benzylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = CH_2Ph), m. p. 215—217° after crystallisation from methanol (Found: C, 85·3; H, 5·05; N, 9·25. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%): 2·6 g.

Action of Acetyl and Benzoyl Cyanides on the Indole (III).—These reagents were freshly prepared and carefully purified before use. Old samples, particularly of benzoyl cyanide, even if carefully redistilled, did not give consistent results.

The following selected experiments typify the results obtained under different conditions. The products were identified by mixed m. p. determinations with compounds prepared as described above.

Acetyl cyanide. (1) (*a*) Acetyl cyanide (0·72 c.c., 2 mols.) was added to a solution of the indole (1 g.) in chloroform (25 c.c.), which was set aside overnight. Evaporation gave an oil, which when stirred with *cyclo*hexane gave the crude acetamido-compound (IV; R = Me) (1 g.), m. p. 146—156°, increased to 154—156° by crystallisation from ethanol.

(*b*) The above mixture was boiled under reflux for 1 hr. and then evaporated. The gummy residue, when stirred with ethanol, gave the acetamido-compound (0·82 g.), m. p. 155—156·5°.

(2) The above mixture was diluted with a saturated solution (20 c.c.) of hydrogen chloride

[16] Zangg, *J. Amer. Chem. Soc.*, 1946, **68**, 2492.
[17] Sonn and Litten, *Ber.*, 1933, **66**, 1512.

in chloroform, and set aside for 48 hr. The crude yellowish crystals of the hydrochloride of the indoloquinoline (V; R = Me), the deposition of which had soon started, were then collected (0·34 g.), washed with chloroform, dried, and dissolved in hot water (70 c.c.) containing dilute hydrochloric acid (0·1 c.c.), and the solution was filtered into an excess of stirred ammonia solution. The precipitated indoloquinoline (0·23 g.) had m. p. 260—268°, increased to 291—293° by recrystallisation from methanol.

The chloroform filtrate was cautiously evaporated, and a solution of the gummy residue in a minimum of ethanol similarly added to ammonia. The precipitated acetamido-compound (0·88 g.), m. p. *ca.* 140°, when recrystallised from ethanol gave the pure product, pale yellow needles, m. p. 153—154·5°.

Two repetitions of this experiment, in which the volume of chloroform–hydrogen chloride added was 10 and 5 c.c. respectively, gave the indoloquinoline (0·16 and 0·08 g.) and the acetamido-compound (1·05 and 1·1 g.). The purity of the precipitated acetamido-compound increased steadily as the above volume decreased.

(3) The above mixture of the indole (1 g.) and the cyanide (0·72 c.c.) in chloroform was heated at 50° whilst a gentle stream of dry hydrogen chloride was passed through the solution for 15 min. Evaporation gave a yellow residue: its solution in hot water (*ca.* 100 c.c.) was added to ammonia as before. The precipitated mixed bases were dried (0·8 g.) and extracted with boiling benzene (8 c.c.), and the latter was filtered. The residue (0·21 g.), m. p. 240—250°, on recrystallisation from methanol gave the indoloquinoline (V; R = Me), needles, m. p. 293—295°. The benzene filtrate on evaporation left a residue which, on recrystallisation from ethanol, gave the indoloquinazoline (VI; R = Me), m. p. 112—113°. These isomers can thus be readily separated, for the former is almost insoluble in boiling benzene, appreciably soluble in cold ethanol, and only moderately so in cold methanol, whereas the latter is readily soluble in hot benzene and only moderately soluble in cold ethanol.

Addition of aluminium chloride or stannic chloride to the above mixture appeared in general to increase the yield of the indoloquinoline. The use of a vigorous stream of hydrogen chloride left the yield of the quinoline unaffected, but gave an impure sample of the quinazoline.

Benzoyl cyanide. (1) Benzoyl cyanide (0·6 g., 2 mols.) was added to a solution of the indole (0·5 g.) in warm chloroform (7·5 c.c.), which was then heated at 60° for 4 hr. and evaporated. The sticky residue when stirred with ethanol solidified, and when then recrystallised from ethanol gave the benzamido-compound (IV; R = Ph), m. p. 173—175°.

(2) When a solution of the indole (0·5 g.) and the cyanide (0·89 g., 2·5 mols.) in chloroform (20 c.c.) containing pyridine (0·2 c.c.) was boiled under reflux for 2 hr., the compound (IV; R = Ph), m. p. 174—175°, was similarly isolated.

(3) The cyanide (1·3 g.) was added to a solution of the indole (1·04 g.) in chloroform (20 c.c.), which was then heated at 60° whilst a steady stream of hydrogen chloride was passed through for 4 hr. The pale yellow precipitate (1·55 g.) was collected from the cold mixture, dissolved in hot water (160 c.c.) containing concentrated hydrochloric acid (0·2 c.c.), and filtered into aqueous ammonia. The precipitate, when collected, washed with water, dried, and repeatedly recrystallised from benzene (charcoal), gave the indoloquinoline (V; R = Ph) (0·75 g.), pale yellow crystals, m. p. 245—246°. This compound may be dimorphic, for the first samples prepared by this method and recrystallised from toluene had m. p. 202—203° (Found: C, 85·25; H, 4·9; N, 9·4%), whereas later samples prepared by this and by the former method (p. 1326) and recrystallised from benzene had the higher m. p. The low-melting material readily sublimed when heated at 240°/0·005 mm., giving cream-coloured crystals, m. p. 243—244°, and a trace of black residue.

2-o-Aminophenyl-1-methylindole (XV).—(*a*) Potassium (0·4 g.) in *tert.*-butanol (10 c.c.) and methyl benzenesulphonate (1·72 g.) were added in turn to a solution of the indole (III) (2·1 g.) also in *tert.*-butanol (40 c.c.), which was boiled under reflux for 10 min. and the butanol then removed with steam. The reddish tarry residue recrystallised from ethanol: when set aside overnight at 0° it solidified, and then readily sublimed at 150°/0·003 mm., affording the colourless *indole* (XV) (*ca.* 90% yield), m. p. 129° after crystallisation from ethanol (Found: C, 81·0; H, 6·45; N, 12·4. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·35; N, 12·6%). The use of methyl toluene-*p*-sulphonate (1·87 g.) also gave excellent results. The solubility of this indole in chloroform is markedly greater than that of the indole (III).

(*b*) *o*-Aminoacetophenone (5 g.), *N*-methyl-*N*-phenylhydrazine (4·85 c.c.), ethanol (10 c.c.), and acetic acid (0·6 c.c.) were boiled together under reflux for 6 hr., then evaporated under reduced pressure to give an oil which solidified and when recrystallised from light petroleum (b. p. 60—80°) afforded the *methylphenylhydrazone*, bright yellow needles, m. p. 76·5—77°

(Found: C, 74·8; H, 7·1; N, 17·5. $C_{15}H_{17}N_3$ requires C, 75·2; H, 7·1; H, 17·6%). The Fischer cyclisation, using zinc chloride essentially as previously described (p. 1324), then gave the indole (XV), m. p. 132—133°, but the yield was very low: when ethanolic hydrogen chloride was used, the indole was not obtained.

Acyl Derivatives of the Indole (XV).—(1) A solution of the indole (1 g.) in formic acid (8 c.c.) at 0° was evaporated to dryness in a vacuum-desiccator. The residue, m. p. 92—95°, when recrystallised from benzene, gave the 2-o-*formamido-compound* (XVII; R = H), m. p. 99—100° (Found: C, 76·7; H, 5·5; N, 11·5. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). It sublimed unchanged when heated at 0·001 mm.: on exposure to air it slowly became sticky.

(2) The indole (0·4 g.) was dissolved in acetic anhydride (1 c.c.) with cooling, and the solution after 1 hr. was shaken with water (10 c.c.). The residual oil was thoroughly washed in turn with 10% aqueous potassium hydrogen carbonate and water, and dried; it solidified. Careful recrystallisation from 50% aqueous ethanol afforded the 2-o-*acetamido-compound* (XVII; R = Me), colourless crystals, m. p. 96—97° (Found: C, 77·0; H, 6·2; N, 10·9. $C_{17}H_{16}ON_2$ requires C, 77·2; H, 6·05; N, 10·6%). The crystallisation of this compound initially gave considerable trouble: the crude material, unless thoroughly washed, may undergo cyclisation during attempted recrystallisation.

(3) A suspension of the indole (XV) in 10% aqueous sodium hydroxide, when shaken with benzoyl chloride, gave the 2-o-*benzamido-compound* (XVII; R = Ph), m. p. 133—134° after crystallisation from ethanol containing 20% of water (Found: C, 80·85; H, 5·75; N, 8·7. $C_{22}H_{18}ON_2$ requires C, 80·9; H, 5·5; N, 8·6%).

Ethanolic solutions of the acylamino-compounds (XVII; R = H, Me, and Ph) gave no precipitate with cold ethanolic 2:4-dinitrophenylhydrazine containing hydrochloric acid: warming the solutions readily caused the following cyclisation.

Cyclisation to 1′-Methylindolo(3′:2′-3:4)quinolines (XVI).—(1) A solution of the indole (XV) (0·5 g.) in 85% formic acid (3 c.c.) was boiled under reflux for 2 hr., cooled, and poured into water, which when basified with ammonia deposited the colourless *indoloquinoline* (XVI; R = H). This compound was readily soluble in many solvents, and was purified by sublimation at 150°/0·001 mm., which afforded crystals, m. p. 146° (Found: C, 82·6; H, 5·3; N, 12·4. $C_{15}H_{12}N_2$ requires C, 82·6; H, 5·2; N, 12·1%). Similar treatment of the formamido-derivative (XVII; R = H) in formic acid also gave (XVI; R = H), m. p. 144° after sublimation at 150°/0·002 mm., undepressed by admixture with the above sample. When an ethanolic solution of the derivative (XVII; R = H) containing a trace of hydrogen chloride was boiled for 15 min., hydrolysis occurred, and the indole (XV) was recovered, m. p. 122—125°, increased by sublimation at 135°/0·001 mm. to 127—128° (mixed and alone).

(2) A solution of the 2-o-acetamido-compound (XVII; R = Me) in acetic acid containing *ca.* 5% of hydrochloric acid was boiled for a few minutes, and when cooled deposited the colourless hydrochloride of the 1′:2-dimethylindoloquinoline (XVI; R = Me). An aqueous solution of this salt, basified with ammonia, gave the base, colourless needles, m. p. 179—180° after crystallisation from ethyl acetate (Found: C, 82·5; H, 5·8; N, 11·4. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%). Kermack and Smith [1] describe this compound as "characteristic yellow sharp-pointed petal-like crystals, m. p. 173—174°;" their analytical figures indicate an impure product.

(3) A solution of the 2-o-benzamido-compound (XVII; R = Ph) in ethanolic hydrogen chloride was boiled under reflux for 10 min.: working up in the usual way gave the colourless 1′-*methyl-2-phenylindolo*(3′:2′-3:4)*quinoline* (XVI; R = Ph), m. p. 188° (from ethyl acetate) (Found: N, 8·8. $C_{22}H_{16}N_2$ requires N, 9·1%).

1′:2-*Dimethyl- and* 1′-*Methyl-2-phenyl-indolo*(3′:2′-3:4)*quinoline* (XVI; R = Me and Ph) *by the Fischer Cyclisation.*—(1) o-Acetamidoacetophenone *N*-methyl-*N*-phenylhydrazone (XVIII; R = Me) was prepared as the o-amino-analogue (p. 1328). The crude product, which crystallised from the initial reaction mixture in 78% yield on cooling, had m. p. 131—132° after crystallisation from aqueous ethanol. Kermack and Smith [1] give m. p. 131°. A solution of this hydrazone (8 g.) in ethanolic hydrogen chloride (50 c.c.) was boiled under reflux for 7 hr., and the deep red solution, when thoroughly cooled in ice-water, deposited the colourless hydrochloride of the base. This salt, when treated with ammonia, gave the 1′:2-dimethylindoloquinoline (XVI; R = Me) (1·7 g., 23%), m. p. 178° (after crystallisation from ethyl acetate), unchanged on admixture with the previous sample. Kermack and Smith [1] do not give the yield obtained by their phosphorus oxychloride cyclisation.

The deliquescent hydrated hydrochloride of the base could not readily be obtained pure. An ethanolic solution of the base, treated with hydriodic acid, deposited the colourless *hydriodide*,

m. p. 358—360° (decomp.), which was washed with hot ethanol and dried (Found : C, 54·5; H, 4·3. $C_{17}H_{14}N_2,HI$ requires C, 54·5; H, 4·1%); it is insoluble in the usual organic solvents.

(2) *o-Benzamidoacetophenone N-methyl-N-phenylhydrazone* (XVIII; R = Ph), similarly prepared in 71% yield, formed yellow crystals, m. p. 126°, from ethanol (Found : C, 76·8; H, 6·0; N, 11·8. $C_{22}H_{21}ON_3$ requires C, 77·1; H, 6·1; N, 12·2%). Cyclisation by ethanolic hydrogen chloride afforded the 1′-methyl-2-phenylindoloquinoline (XVI; R = Ph), which, after crystallisation from light petroleum (b. p. 100—120°) and sublimation at 220°/0·001 mm., had m. p., alone and mixed with the earlier sample, 188° (Found : C, 85·2; H, 5·1; N, 9·0. Calc. for $C_{22}H_{16}N_2$: C, 85·65; H, 5·2; N, 9·1%) : yield 27%.

The hydrated hydrochloride of this base crystallised readily from its solution in hydrochloric acid, but attempted dehydration always caused some dissociation of the salt. A solution of the base in chloroform, when treated with hydrogen chloride and evaporated, gave the anhydrous colourless *hydrochloride*, m. p. 288—292° (decomp.; immersed at 275°) (from dimethylformamide) (Found : C, 76·1; H, 5·3; N, 8·3. $C_{22}H_{16}N_2,HCl$ requires C, 76·6; H, 4·9; N, 8·1%).

Action of Acyl Cyanides on the Indole (XV).—*Acetyl cyanide.* (1) Basic conditions. The cyanide (0·15 c.c.; 1·1 mol.) was added to a solution of the indole (0·44 g.) in chloroform (5 c.c.) containing pyridine (0·1 c.c.), which was set aside overnight, and then evaporated. A solution of the residual oil in 50% aqueous ethanol deposited the acetamido-compound (XVII; R = Me), m. p. 96—97° after further recrystallisation (Found : N, 10·8%). A repetition of this experiment with solely pyridine as a solvent gave the same product.

(2) Neutral conditions. The above mixture, but without addition of pyridine, when similarly set aside, deposited colourless crystals of the acetate of the indoloquinoline (XVI; R = Me), m. p. 338—340° : this salt, treated with ammonia, gave the base, m. p. 176—177°, after crystallisation from ethyl acetate. The mother-liquor from which the acetate separated furnished no other crystalline compound.

(3) Acidic conditions. Hydrogen chloride was passed for 2—3 min. through the above mixture of cyanide and indole in chloroform, which by next day had deposited the hydrochloride of the indoloquinoline in almost theoretical yield; when worked up as in (2) above, it also furnished the pure base. When hydrogen chloride was passed through the above mixture for 1 hr., the solution became dark red and deposited an intractable tar.

Benzoyl cyanide. (1) Basic conditions. (*a*) Pyridine (0·2 c.c.) was added to a solution of the indole (0·44 g.) and the cyanide (0·8 g., 2·5 mols.) in chloroform, which was boiled under reflux for 2 hr., and evaporated. The residue, recrystallised from ethanol, gave the benzamido-compound (XVII; R = Ph), m. p. 132—134°.

(*b*) A solution of the indole (0·44 g.) and the cyanide (0·3 g., 1·1 mols.) in pyridine (5 c.c.) was boiled for 1 hr. and poured into water (50 c.c.). The precipitated solid, recrystallised as before, gave the benzamido-compound, m. p. 132—133°. Repetition of this experiment, using the cyanide (0·8 g.) with boiling for 2 hr., gave the same result.

(2) Neutral conditions. A solution of the indole (0·44 g.) and the cyanide (0·3 g.) in chloroform (5 c.c.) was set aside for 2 days, and the solvent then removed. The gummy residue, when stirred with ethanol, gave the crystalline benzamido-compound (0·5 g.), m. p. 132—133° after recrystallisation (Found : N, 8·6%). A similar mixture, when boiled for 1 hr., gave the same result.

(3) Acidic conditions. Hydrogen chloride was passed for 5 min. through a solution of the indole (0·6 g.) and the cyanide (0·4 g.) in chloroform (10 c.c.), which was then boiled under reflux for 3 hr., filtered to remove a trace of insoluble matter, and evaporated. The solid residue when stirred with acetone to dissolve a brown, tarry impurity, consisted of the hydrochloride of the indoloquinoline (XVI; R = Ph). Decomposition with ammonia gave the free base (0·5 g.), m. p. 188° after crystallisation from ethyl acetate (Found : N, 9·35%). No other products could be isolated. Repetition of this experiment, in which the mixture was set aside for 48 hr. instead of being boiled, gave the same result.

In all the above experiments it is particularly essential to use freshly prepared benzoyl cyanide to obtain consistent results.

Infrared Data.—The benzamido-compound (IV; R = Ph), m. p. 176°, in a Nujol mull shows strong bands at 5·98 and 2·98 μ due to the ·CO and ·NH groups respectively, with weaker bands at 6·17 and 6·32 μ assigned to the amide group; in carbon tetrachloride solution, it shows a strong ·CO band at 5·90 μ and a weak band at 5·98 μ, and a weak band at 2·88 μ due to the ·NH group. These values are closely similar to those of phenylbenzamide, which in the mull shows strong bands at 6·03 and 2·99 μ, and at 6·24 and 6·33 μ, and the tetrachloride solution shows a strong band at 5·91 and 2·90 μ. The isomeric benzamido-compound, m. p. 167°,

probably (VIII; R = Ph), in the mull shows three strong bands at 5·89 and 5·95, and at 2·96 μ, and in the solution a strong and a weak band at 5·89 and 2·93 μ respectively. All the tetrachloride solutions were necessarily very dilute. The 1-methyl-benzamido-compound (XVII; R = Ph) in the mull shows strong bands at 6·00, 6·07, and 3·05 μ, and a weak and a strong band at 6·19 and 6·33 μ: in the tetrachloride solution, it shows strong bands at 5·91 and 2·94 μ, and in hexachlorobutadiene solution, a strong band at 3·05 μ.

It is noteworthy that 3-benzoyl-2-methylindole in the mull shows a weak and a strong band at 6·26 and 6·37 μ, with none in the normal :CO region and only a faint inflection in the normal :NH region; in the tetrachloride solution it shows strong :CO and :NH bands at 6·08 and 2·87 μ. The crystalline indole must therefore show considerable intermolecular hydrogen bonding.

We are indebted to Mr. A. S. Staunton for preliminary work on the preparation of the indole (XV) and its conversion into quinoline (XVI; R = Me). We are also greatly indebted to the Government of Singapore for the award of a Queen's Fellowship (to K. A. K.) and to Imperial Chemical Industries Limited, Dyestuffs Division, for a grant (to A. F. P.) and for various intermediate compounds.

University Chemical Laboratory, Cambridge.
Imperial Chemical Industries Limited, Dyestuffs Division,
Blackley, Manchester. [*Received, October 26th*, 1955.]

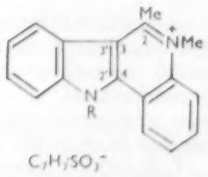
269. *Cyanine Dyes derived from 2-Methylindolo(3′ : 2′-3 : 4)quinoline.*

By Frederick G. Mann and A. F. Prior.

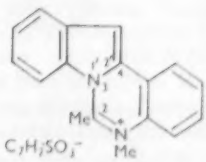
The above indoloquinoline and its 1′ : 2-dimethyl homologue readily give quaternary salts in which the reactive 2-methyl group will condense with suitable heterocyclic systems to give cyanine and azadimethincyanine salts. The properties of certain of these salts, as photographic sensitisers or desensitisers, have been investigated.

In an earlier paper,[1] we described the synthesis of 2-methylindolo(3′ : 2′-3 : 4)quinoline and the isomeric 2-methylindolo(1′ : 2′-3 : 4)quinazoline. These compounds undergo ready quaternisation with methyl toluene-*p*-sulphonate to give 1 : 2-dimethylindolo-(3′ : 2′-3 : 4)quinolinium and 1 : 2-dimethylindolo(1′ : 2′-3 : 4)quinazolinium toluene-*p*-sulphonate, (I; R = H) and (II) respectively. The corresponding 1 : 1′ : 2-trimethyl derivative (I; R = Me) has also been prepared.

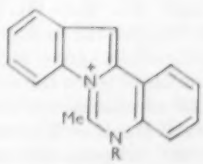
Two noteworthy points arise concerning these series of compounds. First, the quinoline and quinazoline bases corresponding to (I) and (II) are colourless and very pale yellow respectively: the salts of the quinoline base, obtained by neutralisation with acids or by



(I)



(II)



(IIA)

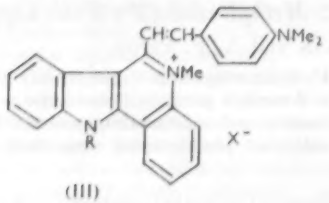
quaternisation (as I) are also colourless, but the corresponding salts of the quinazoline base (as II) are bright yellow. This indicates that the quinazolinium cation receives a considerable contribution from the form (II*A*; R = H or alkyl), whereas the quinolinium cation apparently receives a very small contribution from the form analogous to (II*A*).

Secondly, the 2-methyl group in the quinoline salt (I) should have high reactivity and thus with suitable reagents should form cyanine dyes: on the other hand, the 2-methyl group in quaternised pyrimidines and quinazolines very seldom shows this type of activity. We have prepared a number of cyanine dyes from the salts of type (I) but, as expected,

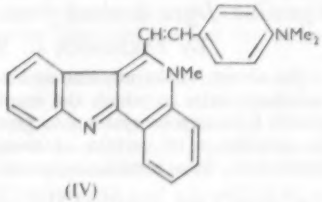
[1] Kiang, Mann, Prior, and Topham, preceding paper.

have failed with the salt (II). Furthermore, the 1 : 2-dimethylindolo(3′ : 2′-3 : 4)-quinolinium cation in (I) is, apart from other substituents, isomeric with the 1 : 2-dimethylindolo(3′ : 2′-3 : 4)*iso*quinolinium cation,* from which Huang-Hsinmin and Mann [2] prepared several cyanine dyes: comparison of the two series is of particular interest, because in the *iso*quinoline series cyanine salt formation was sometimes followed by loss of the 1-methyl group, *i.e.*, by "dequaternisation," to give a covalent compound.

In almost all cases, more rapid condensation and higher yields were obtained from the salt (I; R = Me) than from (I; R = H). Thus the salt (I; R = H) condensed with *p*-dimethylaminobenzaldehyde in acetic anhydride–triethylamine [3] to give [1-methylindolo(3′ : 2′-3 : 4)-2-quinoline][*p*-dimethylaminobenzene]dimethincyanine toluene-*p*-sulphonate (III; R = H, X = $C_7H_7{\cdot}SO_3$) but only in very low yield. Condensation by prolonged boiling in methanol–piperidine gave yellow needles of a stable monomethanol solvate of composition $C_{25}H_{21}N_3{,}CH_4O$ or $C_{26}H_{23}N_3{,}CH_4O$, formed by the loss of methyl or hydrogen toluene-*p*-sulphonate respectively from (III; R = H, X = $C_7H_7{\cdot}SO_3$). The structure of this compound is uncertain but, by analogy with the azadimethin analogue (VII) discussed below, it is probably the *ψ*-indolo-derivative (IV) formed by loss of toluene-*p*-sulphonic acid; alternatively, it may be the base (III; R = Me, X = OH), formed in turn by the union of methanol with (IV), which would account for its great stability. The use of the salt (I; R = Me) in ethanol–piperidine readily gave the brick-red cyanine (III; R = Me, X = $C_7H_7{\cdot}SO_3$) in 88% yield.

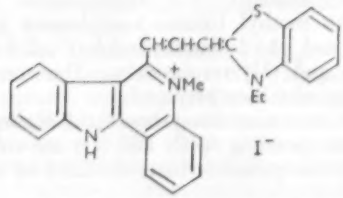


(III)



(IV)

(V)



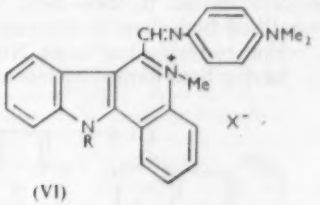
The salt (I; R = H) condensed speedily with 2-2′-acetanilidovinylbenzothiazole ethiodide [4] to give the dark green [1-methylindolo(3′ : 2′-3 : 4)-2-quinoline][3-ethyl-2-benzothiazole]trimethincyanine iodide (V) in 38% yield: exceptionally, no satisfactory product could be isolated when the salt (I; R = Me) was used in this condensation.

The use of suitable nitroso-compounds similarly gave rise to azadimethincyanine salts. Thus the salt (I; R = H) condensed with dimethyl-*p*-nitrosoaniline in methanol-piperidine to give the crimson crystalline salt (VI; R = H, X = $C_7H_7{\cdot}SO_3$). Increasing the proportion of piperidine in this experiment gave dark-red crystals of composition $C_{24}H_{20}N_4$ or $C_{25}H_{22}N_4$, which being solvent-free could be investigated spectroscopically. Loss of methyl toluene-*p*-sulphonate from the above salt would give the base (VII*A*), whilst loss of toluene-*p*-sulphonic acid would give the methylated compound (VII*B*). The infrared spectrum of this product, in a Nujol and a hexachlorobutadiene mull, showed no indication of an :NH band in the 2·9 μ region, and the compound is therefore (VII*B*). This conclusion

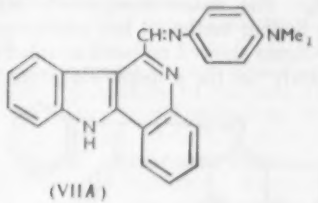
* It is noteworthy that this cation is also yellow (although the parent base is colourless) and thus resembles the cation in the salt (II) and not that in (I).

[1] Huang-Hsinmin and Mann, *J.*, 1949, 2911.
[2] Hamer, Rathbone, and Winton, *J.*, 1949, 21.
[3] Brooker, White, Keyes, Smyth, and Oesper, *J. Amer. Chem. Soc.*, 1941, **63**, 3201.

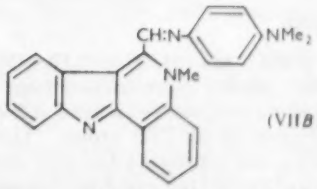
is confirmed by the fact that this compound readily combined with toluene-*p*-sulphonic acid to re-form the salt (VI; R = H, X = $C_7H_7{\cdot}SO_3$).*



(VI)



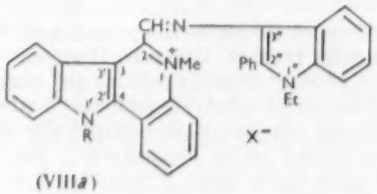
(VII*A*)



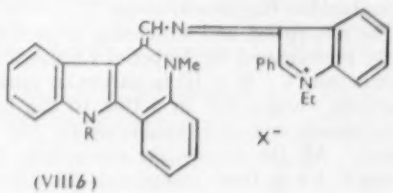
(VII*B*)

It is of interest that charge separation could occur in the compound (VII*A*) by either the :NH or the ·NMe_2 group's becoming positively charged, the quinoline-nitrogen atom in each case taking the negative charge, and in (VII*B*) by the ·NMe_2 or the :NMe group's becoming positively charged, the pyrrole-nitrogen now becoming in each case negatively charged. Both compounds are thus of the general *mero*cyanine type.

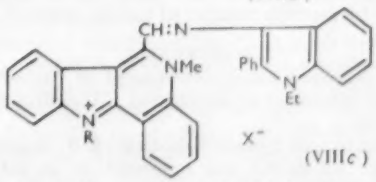
The salt (I; R = Me) reacted with dimethyl-*p*-nitrosoaniline, to give solely the 1 : 1′-dimethylcyanine salt (VI; R = Me, X = $C_7H_7{\cdot}SO_3$) in 62% yield.



(VIII*a*)



(VIII*b*)



(VIII*c*)

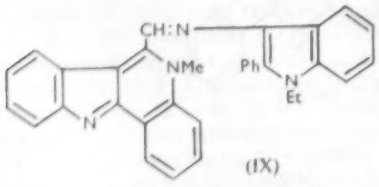
Particular interest attaches to the cyanine salts obtained by condensation with 3-nitrosoindoles. The salt (I; R = H) reacted very readily with 1-ethyl-3-nitroso-2-phenylindole [5] in acetic anhydride–triethylamine to form the scarlet cyanine toluene-*p*-sulphonate (VIII; R = H, X = $C_7H_7{\cdot}SO_3$) in 62% yield: the salt (I; R = Me) gave the corresponding 1 : 1′-dimethyl derivative (VIII; R = Me, X = $C_7H_7{\cdot}SO_3$). These salts, like the analogous compounds recorded by Huang-Hsinmin and Mann,[2] differ from most cyanine salts, inasmuch as the positive charge can now be carried by the three nitrogen atoms (as in VIII*a*, *b*, and *c*) instead of the usual two atoms.

The salt (I; R = H) did not apparently condense with the above nitrosoindole when a methanol–piperidine solution was boiled for 24 hr. Condensation occurred however when

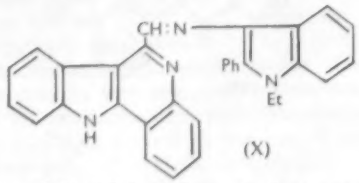
* For other examples of polycyclic ψ-indoles, and their reaction with acids and alkyl halides, see Mann, *J.*, 1949, 2816; Almond and Mann, *J.*, 1952, 1870; Braunholtz and Mann, *J.*, 1955, 381.

[5] Crowther, Mann, and Purdie, *J.*, 1943, 58; Mann and Haworth, *J.*, 1944, 670.

a solution of the reagents in methanol containing sodium methoxide was boiled for 50 hr., giving two products of almost identical composition, corresponding to the formula $C_{32}H_{24}N_4$ or $C_{33}H_{26}N_4$. The minor component, orange crystals, m. p. 295—297°, was almost insoluble in boiling methanol but readily recrystallised from dimethylformamide, and its infrared spectrum showed no band in the 2·9 μ region corresponding to an :NH group: it almost certainly has the *ψ*-indolo-structure (IX), having been formed by loss of toluene-*p*-



(IX)



(X)

sulphonic acid from the salt (VIII; R = H, X = $C_7H_7{\cdot}SO_3$). The second component, yellow crystals, m. p. 261—264°, readily recrystallised from methanol, and the infrared spectrum of the thoroughly dried material showed a band at 2·95 μ, in both Nujol and hexachlorobutadiene mull, characteristic of an :NH group. There is little doubt that this compound has the structure (X), and represents the only authenticated example of true "dequaternisation," due to loss of methyl toluene-*p*-sulphonate, encountered in the present series.

Using 1 : 2-dimethyl-1′-phenylindolo(3′ : 2′-3 : 4)*iso*quinolinium iodide, Huang-Hsinmin and Mann [2] found that dequaternisation with loss of methyl iodide accompanied the condensation with dimethyl-*p*-nitrosoaniline and 3-nitroso-1 : 2-diphenylindole, but not that with *p*-dimethylaminobenzaldehyde and 1-ethyl-3-nitroso-2-phenylindole. Clearly, in these condensations, the presence of the 1′-phenyl group in the indolo*iso*quinoline salt would prevent any reaction comparable with the loss of toluene-*p*-sulphonic acid encountered in the present series.

The absorption and sensitising properties of some of the above compounds have been kindly investigated by Imperial Chemical Industries Limited, Dyestuffs Division. The cyanine salt (V; R = H) in particular ranks as a good sensitiser in positive and negative emulsions, comparable in action to the better known [1-*n*-butyl-2-quinoline][3-ethyl-2-benzothiazole]trimethincyanine iodide, but it does not sensitise in photographically useful regions. All the azamethin compounds tested proved to be desensitisers: this was expected, for in these compounds the nitrogen atom in the chain is separated from the heterocyclic nitrogen atoms by an even number of carbon atoms.[6] For details, see p. 1336.

Experimental

The cyanine derivatives described below were heated at 70—80°/0·2 mm. before analysis, but certain members retained solvent of crystallisation. This firm adherence of solvent occurs in many types of cyanine salts.

Quaternisation.—(1) A mixture of 2-methylindolo(3′ : 2′-3 : 4)quinoline (2·1 g.) and methyl toluene-*p*-sulphonate (2·1 g., 1·2 mols.) was immersed in an oil-bath and stirred with a thermometer: at 125° a vigorous reaction occurred with effervescence, the temperature rose to 150° and the melt solidified. A mixture of the cold pulverised melt and ethanol (20 c.c.) was boiled to extract much gummy impurity, and the insoluble *quinolinium* salt (I; R = H) was collected, washed with hot ethanol, and dried (yield, 2·0 g., 53%). Recrystallisation from much methanol gave the pure salt, as needles, m. p. 298—300° (decomp.) (Found: C, 69·3; H, 5·4; N, 6·6. $C_{24}H_{22}O_3N_2S$ requires C, 68·9; H, 5·3; N, 6·7%): solutions in methanol and in water had a blue fluorescence.

(2) The 1′ : 2-dimethylindoloquinoline, similarly treated, also gave a melt which solidified, and when triturated with ether to remove unchanged sulphonate yielded the crude *quinolinium* salt (I; R = Me) in theoretical yield. Recrystallisation from ethanol gave prisms, m. p. 243—244°, also giving a blue fluorescence in ethanol and in water (Found: C, 68·75; H, 5·5; N, 6·3. $C_{25}H_{24}O_3N_2S$ requires C, 69·6; H, 6·0; N, 6·45%).

(3) A similar mixture of 2-methylindolo(1′ : 2′-3 : 4)quinazoline, heated as before, melted at

[6] Kendall, *J. Soc. Dyers and Colourists*, 1936, **52**, 13.

100—110° and underwent a vigorous reaction, the temperature rising to 140° and the bright yellow melt solidifying. The melt was extracted with ether as in (2), and the residue, when recrystallised from ethanol, afforded the pure *quinazolinium* salt (II), large lemon-coloured prisms (68%), m. p. 258—260°, readily soluble in cold water giving a non-fluorescent bright yellow solution (Found: C, 69·0; H, 5·15. $C_{24}H_{22}O_3N_2S$ requires C, 68·9; H, 5·3%).

Cyanines.—[1-*Methylindolo*(3′ : 2′-3 : 4)-2-*quinoline*][p-*dimethylaminobenzene*]*dimethincyanine toluene*-p-*sulphonate* (III; R = H, X = $C_7H_7{\cdot}SO_3$). A mixture of the salt (I; R = H) (0·21 g.), *p*-dimethylaminobenzaldehyde (0·1 g., 1·5 mols.), acetic anhydride (10 c.c.), and triethylamine (0·2 c.c., *ca.* 2 mols.) was boiled under reflux for 1 hr.: after 10 min. a clear brownish-red solution was obtained. The solution was poured into water (50 c.c.), the crude cyanine, m. p. 305° (decomp.), being precipitated in very low yield. Many variations in conditions of reaction and isolation gave no better yield: the united product from these experiments, when recrystallised from methanol, afforded the *cyanine* (III; R = H, X = $C_7H_7{\cdot}SO_3$), orange-red needles, m. p. 307—308° (decomp.) (Found: C, 71·3; H, 5·5. $C_{33}H_{31}O_3N_3S$ requires C, 71·8; H, 5·6%).

A solution of the salt (I; R = H) (0·85 g.) and the aldehyde (0·45 g., 1·5 mols.) in methanol (40 c.c.) and piperidine (0·15 c.c.) was boiled under reflux for 24 hr., concentrated to half-bulk, and set aside overnight at 0°. The crude crystalline deposit, when recrystallised from methanol, gave yellow needles, m. p. 263—265° to a bright red liquid, presumably *dimethin*-2-[1-*methyl*-ψ-*indolo*(3′ : 2′-3 : 4)*quinoline*][p-*dimethylaminobenzene*] *monomethanol solvate* (IV) [alternatively named as solvate of 2-p-*dimethylstyryl*-1-*methyl*-ψ-*indolo*(3′ : 2′-3 : 4)*quinoline*] (Found: C, 79·2; H, 5·9; N, 10·8. $C_{26}H_{23}N_3,CH_4O$ requires C, 79·2; H, 6·6; N, 10·3. $C_{25}H_{21}N_3,CH_4O$ requires C, 79·0; H, 6·4; N, 10·6%). The presence or absence of an :NH group could not be determined with certainty by infrared spectroscopy, owing to the hydroxyl band of the methanol; the name given above applies to the C_{26} compound.

The 1 : 1′-*dimethylcyanine sulphonate* (III; R = Me, X = $C_7H_7{\cdot}SO_3$). A mixture of the salt (I; R = Me) (0·87 g.) and *p*-dimethylaminobenzaldehyde (0·45 g., 1·5 mols.) in ethanol (40 c.c.) and piperidine (0·25 c.c.), when boiled for 30 hr., concentrated, and cooled to 0°, slowly deposited the *cyanine monoethanol solvate* (III; R = Me, X = $C_7H_7{\cdot}SO_3$), bright red prisms with a yellow reflex, m. p. 266—267° after recrystallisation from ethanol (Found: C, 71·3; H, 6·3; N, 7·0. $C_{34}H_{33}O_3N_3S,C_2H_6O$ requires C, 71·3; H, 6·4; N, 6·9%). One much smaller preparation gave the *monohydrate*, of identical m. p. (Found: C, 72·9; H, 6·45. $C_{34}H_{33}O_3N_3S,H_2O$ requires C, 72·5; H, 6·45%).

[1-*Methylindolo*(3′ : 2′-3 : 4)-2-*quinoline*][2-*ethyl*-2-*benzothiazole*]*trimethincyanine iodide* (V). A mixture of the salt (I; R = H) (0·21 g.), 2-2′-acetanilidovinylbenzothiazole ethiodide (0·25 g., 1 mol.), ethanol (12 c.c.), and triethylamine (0·2 c.c.) was boiled for 1 hr. and cooled. The crude deposit (0·25 g., 38%), when collected and recrystallised from methanol–pyridine (4 : 1 by vol.), gave the pure *iodide monohydrate*, dark green tablets, m. p. 264° (decomp.) (Found: C, 58·5; H, 4·7; N, 7·7. $C_{28}H_{24}N_3IS,H_2O$ requires C, 58·3; H, 4·5; N, 7·3%). The salt gives permanganate-coloured solutions; that in pyridine has a green fluorescence.

Azadimethin Cyanines.—[1-*Methylindolo*(3′ : 2′-3 : 4)-2-*quinoline*][p-*dimethylaminobenzene*]-β-*azadimethincyanine toluene*-p-*sulphonate* (VI; R = H, X = $C_7H_7{\cdot}SO_3$). A mixture of the salt (I; R = H) (0·85 g.), dimethyl-*p*-nitrosoaniline (0·5 g., 1·5 mols.), methanol (30 c.c.), and piperidine (0·25 c.c.) was boiled for 10 hr., small red crystals separating from the deep red solution. After cooling to 0°, the crude *cyanine sulphonate* (0·40 g., 36%) was collected and recrystallised from much methanol, giving crimson crystals, m. p. 310—311° (decomp.; immersed at 295°) (Found: C, 69·5; H, 5·8; N, 10·1. $C_{32}H_{30}O_3N_4S$ requires C, 69·7; H, 5·5; N, 10·2%). Recrystallisation from dimethylformamide gave the salt having the same m. p. No other product could be isolated from the original mother-liquor.

Repetition of this experiment, with twice the quantity of piperidine, gave dark red needles of β-*azadimethin*-2-[1-*methyl*-ψ-*indolo*(3′ : 2′-3 : 4)*quinoline*][p-*dimethylaminobenzene*] (VII*B*) [alternatively named 2-p-*dimethylanilinomethyl*-1-*methyl*-ψ-*indolo*(3′ : 2′-3 : 4-*quinoline*)] (0·21 g., 29%), which did not crystallise from methanol, but from dimethylformamide gave crimson needles, m. p. 281—281·5° (Found: C, 79·0; H, 5·7; N, 14·8. $C_{25}H_{22}N_4$ requires C, 79·3; H, 5·9; N, 14·8%). No other crystalline compound could be isolated. A solution of this product (32 mg.) and toluene-*p*-sulphonic acid (21 mg., 1·2 mols.) in dimethylformamide (20 c.c.) was gently boiled for 10 min., and when cooled deposited deep red crystals, which after one recrystallisation from this solvent had m. p. 309° (decomp.), undepressed on admixture with the authentic salt (VI; R = H, X = $C_7H_7SO_3$) of m. p. 310—311° (decomp.), both immersed at 295°.

The 1 : 1′-*dimethylindolocyanine sulphonate monohydrate* (VI; R = Me, X = $C_7H_7{\cdot}SO_3$) was prepared in the same way as the sulphonate (VI; R = H), but from the salt (I; R = Me) in ethanol with 7 hours' boiling (62% yield): it separated from ethanol in scarlet prisms with a yellow reflex, m. p. 275—276° (decomp.; immersed at 265°) (Found: C, 69·1; H, 6·1; N, 9·7. $C_{33}H_{32}O_3N_4S,H_2O$ requires C, 68·6; H, 5·9; N, 9·65%).

[1-*Methylindolo*(3′ : 2′-3 : 4)-2-*quinoline*][1″-*ethyl*-2″-*phenyl*-3″-*indole*]-β-*azadimethincyanine toluene*-p-*sulphonate* (VIII*a*—*c*; R = H, X = $C_7H_7{\cdot}SO_3$). A solution of the salt (I; R = H) (0·21 g.) and 1-ethyl-3-nitroso-2-phenylindole (0·15 g., 1·5 mols.) in hot acetic anhydride (10 c.c.) was treated with triethylamine (0·2 c.c., 2 mols.) and boiled for 15 min. The blood-red solution, on cooling, deposited the *cyanine sulphonate monohydrate* (0·2 g., 62%), scarlet needles, m. p. 255—257° after crystallisation from dimethylformamide (Found: C, 71·8; H, 5·4. $C_{46}H_{34}O_3N_4S,H_2O$ requires C, 72·1; H, 5·4%). Increasing the scale of this experiment did not give a corresponding increase in the yield.

When the salt (I; R = H) (0·65 g.) and the indole (0·55 g., 1·5 mols.) were added to the product from the interaction of sodium (20 mg.) and methanol (25 c.c.), which was then boiled for 50 hr. and cooled, a mixed crop of crystals appeared. These were collected and extracted with boiling methanol. The undissolved residue (78 mg.), when crystallised from dimethylformamide, gave β-*azadimethin*-2-[1-*methyl*-ψ-*indolo*(3′ : 2′-3 : 4)*quinoline*]-3″-[1″-*ethyl*-2″-*phenylindole*] (IX) [alternatively named 2-(1-*ethyl*-2-*phenyl*-3-*indolyliminomethyl*)-1-*methyl*-ψ-*indolo*-(3′ : 2′-3 : 4)*quinoline*], orange needles, m. p. 295—297° (decomp.) (Found: C, 82·1; H, 6·0; N, 11·9. $C_{33}H_{26}N_4$ requires C, 82·7; H, 5·5; N, 11·7%). The methanolic extract, when worked up, yielded β-*azadimethin*-2-[*indolo*(3′ : 2′-3 : 4)*quinoline*]-3″-[1″-*ethyl*-2″-*phenylindole* (X) (alternatively named analogously to (IX)] (0·15 g.), yellow crystals, m. p. 261—264° to a deep red liquid, after recrystallisation from much methanol (Found: C, 82·2; H, 6·0; N, 11·8. $C_{33}H_{24}N_4$ requires C, 82·7; H, 5·2; N, 12·05%). The infrared spectrum of this compound has a band at 2·95 μ: otherwise the spectra of the bases (IX) and (X) are closely similar, and they have a strong band at 6·17 and 6·18 μ respectively, which is in the region in which a band due to the ·CH:N· group would be expected.

The 1 : 1′-*dimethylindolocyanine sulphonate* (VIII*a*—*c*; R = Me, X = $C_7H_7{\cdot}SO_3$) was readily obtained when a solution of the salt (I; R = Me) (0·7 g.) and the indole (0·5 g., 1·1 mols.) in ethanol (25 c.c.) and piperidine (0·25 c.c.) was boiled for 5 hr., concentrated, and cooled to 0°. The deposited sulphonate (0·65 g., 61%), when recrystallised from ethanol, formed deep red prisms with a yellow reflex, m. p. 254—255° (Found: C, 73·75; H, 5·2; N, 8·5. $C_{41}H_{34}O_3N_4S$ requires C, 74·0; H, 5·4; N, 8·5%).

Attempts to form a cyanine salt by the condensation of the salt (I; R = Me) and quinoline-2-aldehyde gave indefinite results.

The absorption and sensitising properties of certain of the above compounds are given in the Table.

Compound	$\lambda_{max.}$ (mμ)	$10^{-4}\varepsilon$	Sensitising max. (mμ)	Sensitising extends to (mμ)	Remarks
(III; R = Me, X = $C_7H_7{\cdot}SO_3$)	444	1·8	~510	615	Weak sensitiser for positive (Cl/Br) emulsions
			550 *	670 *	Rather better in negative (I/Br) emulsions.
(V)	555	8·3	585	640	Good sensitiser in positive and negative emulsions, but does not sensitise in useful region
			~580 *	665 *	
(VI; R = H, X = $C_7H_7{\cdot}SO_3$)	435	1·2	No sensitisation		Desensitiser
(VI; R = Me, X = $C_7H_7{\cdot}SO_3$)	462	1·45	,,		Strong desensitiser
(VII*B*)	417 *	1·45	,,		Moderately strong desensitiser
(VIII; R = H, X = $C_7H_7{\cdot}SO_3$)	462	2·1	,,		Desensitiser
(VIII; R = Me, X = $C_7H_7{\cdot}SO_3$)	450	1·6	,,		Moderately strong desensitiser

The values for $\lambda_{max.}$ were determined in methanolic solution except that for (VII*B*), which was determined in 2-ethoxyethanol. The sensitising maxima were determined in chlorobromide emulsions except those marked *, which were in iodobromide emulsions.

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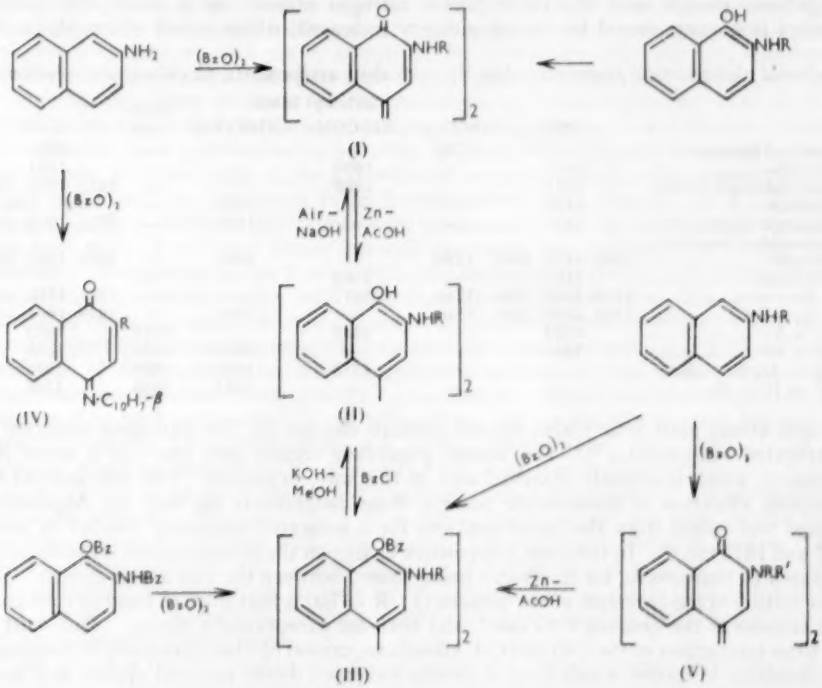
270. *The Oxidation of 2-Naphthylamine with Benzoyl Peroxide.*

By S. F. D. Orr, Peter Sims, and (in part) D. Manson.

The action of benzoyl peroxide on 2-naphthylamine and some related compounds has been investigated, and a number of products identified. The infrared spectra of some of these products are described.

Benzoyl peroxide in chlorobenzene at 80° is known to give rise to free benzoate radicals, and the action of these radicals on polycyclic hydrocarbons has been examined by Roitt and Waters [1,2] in an attempt to understand the relation between the chemical and the biological properties of these compounds. For the same reason we have examined the action of these radicals on the carcinogenic agent, 2-naphthylamine.

The principal product of the oxidation was a high-melting, coloured compound, which, from a consideration of the evidence presented below, appears to be di-(3-benzamido-1 : 4-dihydro-4-oxonaphthylidene) (I; R = Bz). When reduced with zinc and acetic acid, it gave a phenol which was readily re-oxidised by air, particularly in the presence of alkali.



The structure (II; R = Bz) is assigned to it because on hydrolysis it yielded 3 : 3′-diamino-4 : 4′-dihydroxy-1 : 1′-dinaphthyl (II; R = H), and on benzoylation the corresponding tetrabenzoate (III; R = Bz).

The structure of the aminophenol (II; R = H) was proved by its synthesis by an independent route: 4 : 4′-dihydroxy-1 : 1′-dinaphthyl was treated with nitrous acid to yield a dinitroso-compound, which, because the positions *para* to the hydroxyl groups are

[1] Roitt and Waters, *J.*, 1952, 2695.
[2] Cf. Perret and Perrot, *Helv. Chim. Acta*, 1945, **28**, 558.

blocked, should be 4 : 4′-dihydroxy-3 : 3′-dinitroso-1 : 1′-dinaphthyl. The dinitroso-compound was reduced with sodium dithionite to the diamine (II; R = H). The amino-groups must be *ortho* to the hydroxyl groups in this compound for its tetrabenzoate, identical with that given by the phenol (II; R = Bz) above, was also formed by reaction of 2-benzamido-1-naphthyl benzoate with benzoyl peroxide in chlorobenzene. The benzoate therefore has the structure (III; R = Bz) and this is confirmed by its infrared absorption which is almost identical with that of 2-benzamido-1-naphthyl benzoate itself in the NH and C=O stretching regions (Table). The subsidiary peaks at about 3420 and 3393 cm.$^{-1}$ on the low-frequency side of the main NH stretching band, absent in the simple derivatives, arise from forms showing weak intramolecular hydrogen bonding,[3,4] proving the benzoyloxy- and benzamido-groups to be *ortho* to one another in both compounds. For the same reason, the benzoyl-carbonyl band is broader in the mixed compounds than in 1-naphthyl benzoate.

The most likely structure for the coloured compound, therefore, is that formulated above (I; R = Bz), and this is supported from its infrared spectrum (Table), although the exceptionally low NH frequency of 3363 cm.$^{-1}$ and the position of the quinone band require some discussion. The latter, by comparison with that of diphenoquinone [5] at 1635 cm.$^{-1}$ and analogy with the benzoquinone series,[6] might be expected at about 1642 cm.$^{-1}$. The lower frequency observed can be explained by the interaction, through conjugation, of the quinone groups with the nucleophobic nitrogen atoms. As a result, the amide-carbonyl frequency should be correspondingly increased, which is not observed, or the

Infrared characteristic frequencies (cm.$^{-1}$), with their assignments, in chloroform solution.

		Carbonyl bands			Quin-	
	>NH	–O·CO·Ar	–NH·COMe	–NH·CO·Ar	one	C=C
1-Naphthyl benzoate	—	1739	—	—	—	1601
Acetanilide	3437	—	1690	—	—	1601
2-Acetamidonaphthalene	3437	—	1689	—	—	1632, 1605, 1585
Benzanilide	3436	—	—	1676	—	1601, 1584
2-Benzamidonaphthalene	3437	—	—	1676	—	1635, 1603, 1584
2-Benzamido-1-naphthyl benzoate	3440, 3422, 3393	1740	—	1680	—	1638, 1607, 1583
Diacetamide	3400	—	1708	—	—	—
III; R = Ac	3439, 3423, 3384	1744	1697	—	—	1629, 1610, 1585
III; R = Bz	3440, 3420, 3393	1740	—	1681	—	1626, 1604, 1585
I; R = Ac	3363	—	1692	—	1619	1603
I; R = Bz	3361	—	—	1674	1620	1596
V; R = Ac, R′ = Bz	—	—	1715	1695	1634	1595
V; R = R′ = Bz	—	—	—	1694	1633	1594

nitrogen atoms must bear higher overall positive charges (cf. the analogous situation in unsaturated ester-nitriles [7]). The second possibility should give rise [8] to a lower NH frequency, which is actually observed and, in this way, explained. The NH and the CO stretching vibration of diacetamide confirm these assignments for they are respectively lowered and raised from the usual positions for a saturated secondary amide [9] of about 3437 and 1675 cm.$^{-1}$. In this case, the positive charge on the nitrogen atom is insufficiently increased to compensate for its effect's being shared between the two acetyl groups. One other feature of the spectrum of the quinone (I; R = Bz) is that the C=C band at 1596 cm.$^{-1}$ is as intense as the quinone C=O band, and both are exceptionally strong. This must be due to an interaction of the C=O and C=C vibrations, caused by their proximity in frequency, and resulting in modes which have a greatly increased dipole moment change and hence absorption intensity.

The mode of formation of the quinone (I; R = Bz) seems reasonably certain. In the oxidation of *N*-alkylanilines with benzoyl peroxide, Edward [10] postulated that the action

[3] Mizushima, Shimanouchi, Tsuboi, Sugita, Kato, and Kondo, *J. Amer. Chem. Soc.*, 1951, **73**, 1330.
[4] Mizushima, Tsuboi, Shimanouchi, and Asai, *ibid.*, 1954, **76**, 6003.
[5] Fuson, Josien, and Shelton, *ibid.*, p. 2526.
[6] Josien, Fuson, Lebas, and Gregory, *J. Chem. Phys.*, 1953, **21**, 331.
[7] Felton and Orr, *J.*, 1955, 2170.
[8] Fuson, Josien, Powell, and Utterbach, *J. Chem. Phys.*, 1952, **20**, 145.
[9] Richards and Thompson, *J.*, 1947, 1248.
[10] Edward, *J.*, 1954, 1464.

of the benzoate radicals leads first to the removal of hydrogen from the amino-groups to yield mesomeric radicals of the type :

These then react with benzoate radicals in the nucleus in positions *ortho* to the amino-groups. In the *o*-benzoyloxyamino-compounds thus formed, however, *ortho*-*O* ⟶ *N* migrations of acyl groups readily take place (the reduction of *o*-nitrophenyl benzoate, for example, yields *o*-benzamidophenol [11]). A similar mechanism in the case of 2-naphthylamine would lead to the initial formation of 2-amino-1-naphthyl benzoate, followed by rearrangement to 2-benzamido-1-naphthol. Abstraction of hydrogen from this compound, followed by dimerisation in the 4-position, should then yield the product (I; R = Bz). When 2-benzamido-1-naphthol was treated with benzoyl peroxide in chlorobenzene, the quinone (I; R = Bz) was formed and, under similar conditions, 2-acetamido-1-naphthol yielded a coloured compound which probably has the structure (I; R = Ac). The infra-red spectrum of this compound was analogous to that of the benzamido-compound already discussed. The 1692 cm.$^{-1}$ band is due to the acetamido-carbonyl group, while the low quinone frequency of 1619 cm.$^{-1}$, intensified by interaction with the C=C frequency of 1603 cm.$^{-1}$, is again accompanied by a low NH frequency of 3363 cm.$^{-1}$.

Among the other products of the oxidation of 2-naphthylamine were 2 : 2′-azonaphthalene and 1 : 2-5 : 6-dibenzophenazine, the latter being a well-known product of the oxidation of 2-naphthylamine by other methods.[12,13] Edward [14] has also obtained compounds of these types in the oxidation of aromatic amines with benzoyl peroxide. Another product was considered to be 2-benzamido-1 : 4-naphthaquinone 4-2′-naphthylimide (IV; R = NHBz). Hydrolysis with potassium hydroxide in methanol yielded the free base (IV; R = NH_2), whose infrared spectrum was identical with that of the 2-amino-1 : 4-naphthaquinone 2′-naphthylimide obtained by Teuber and Jellinek [15] in the oxidation of 2-naphthylamine with potassium nitrosodisulphonate. The free base was converted by acetic anhydride into the acetyl derivative (IV; R = NHAc) which had the same properties as those of a compound obtained by Pausacker and his co-workers [16] in the oxidation of 2-naphthylamine with phenyl iodosoacetate or lead tetra-acetate, and of 2-acetamidonaphthalene with phenyl iodosoacetate. These workers considered their compound to be 2-acetamido-1 : 4-naphthaquinone 1-2′-naphthylimide, but because 2-2′-naphthylamino-1 : 4-naphthaquinone 4-2′-naphthylimide (IV; R = NH·$C_{10}H_7$-β) was obtained when the free base (IV; R = NH_2) was heated with 2-naphthylamine in acetic acid, it seemed to us more likely that our imide was 2-benzamido-1 : 4-naphthaquinone 4-2′-naphthylimide. The imide (IV; R = NH·$C_{10}H_7$-β), which was also isolated in the oxidation of 2-naphthylamine with persulphate,[12] has been synthesised by Meldola [17] from 2 : 4-dibromo-1-naphthol and 2-naphthylamine. The further action of the mesomeric radicals already mentioned can account for the formation of the above oxidation products.

A number of other coloured products were formed in the oxidation of 2-naphthylamine, but these were not further examined.

The action of benzoyl peroxide on 2-acetamido- and 2-benzamido-naphthalene was also investigated. The reactions were much less vigorous than in the case of 2-naphthylamine itself, and some difficulty was experienced in separating the products. 2-Acetamido- and 2-benzamido-1-naphthyl benzoate were not isolated, but when the products from the

[11] Böttcher, *Ber.*, 1883, **16**, 629.
[12] Boyland, Manson, and Sims, *J.*, 1953, 3623.
[13] Clemo and Dawson, *J.*, 1939, 1114.
[14] Edward, *J.*, 1956, 222.
[15] Teuber and Jellinek, *Chem. Ber.*, 1954, **87**, 1841.
[16] Barlin, Pausacker, and Riggs, *J.*, 1954, 3122; Barlin and Riggs, *ibid.*, p. 3125; Pausacker and Scroggie, *ibid.*, p. 4003.
[17] Meldola, *J.*, 1884, 156.

oxidation of 2-benzamidonaphthalene were chromatographed on alumina a little 2-phenylnaphth-2 : 1-oxazole was obtained. This oxidation also gave 2 : 2′-dibenzamido-1 : 1′-dinaphthyl in good yield, together with the tetrabenzoate (III; R = Bz) described above. The oxidation of 2-acetamidonaphthalene yielded a compound which, because it afforded 3 : 3′-diamino-4 : 4′-dihydroxy-1 : 1′-dinaphthyl (II; R = H) on hydrolysis, was presumed to be 3 : 3′-diacetamido-4 : 4′-dibenzoyloxy-1 : 1′-dinaphthyl (III; R = Ac). Its infrared spectrum was closely similar to that of the corresponding benzamido-compound (III; R = Bz); the bands at 1744 and 1697 cm.$^{-1}$ are assigned to the benzoate and the acetamido-carbonyl group respectively, and the NH absorption again showed the characteristics of an intramolecularly hydrogen-bonded system.

Oxidations of 2-acetamido- and 2-benzamido-naphthalene each yielded coloured compounds which, on evidence described below, have been formulated as di-(3-*N*-acetylbenzamido-1 : 4-dihydro-4-oxonaphthylidene) (V; R = Ac, R′ = Bz) and di-(3-dibenzoylamino-1 : 4-dihydro-4-oxonaphthylidene) (V; R = R′ = Bz), respectively. These compounds were both reduced by zinc and acetic acid to the derivatives (III; R = Ac and Bz respectively), but the reverse change could not be brought about, either with air or with benzoyl peroxide. Both compounds were unaffected by hot dilute hydrochloric acid but were readily decomposed by potassium hydroxide in methanol in the cold to ammonia and unidentified amorphous substances. When the hydrolyses were stopped after a few minutes by the addition of water, products were extracted into chloroform giving solutions which, on spectrographic analysis, showed maxima at 5750 Å. The compounds (I; R = Ac and Bz) both show maxima at this wavelength. The infrared spectrum of the dibenzoyl derivative (V; R = R′ = Bz) showed bands at 1694 and 1633 cm.$^{-1}$ in chloroform solution which were assigned to the dibenzoylamino- and the quinonoid-carbonyl group respectively. In this compound as formulated above, the nucleophobic nature of the nitrogen is shared with two benzoyl groups as well as with the quinonoid-carbonyl group. The frequency of the latter would therefore be expected to be reduced much less than in the monobenzoyl compound (I; R = Bz); at the same time the *N*-benzoyl-carbonyl frequency should be considerably higher than for a normal benzanilide type of compound. In the spectrum of the compound formulated as (V; R = Ac, R′ = Bz) analogous absorption bands were found and similar assignments made. In this case the upper band is split into two components as would be expected for a mixed acetyl-benzoyl compound, for the acetyl-carbonyl group should absorb at some 20 cm.$^{-1}$ higher than the benzoyl. In neither case was absorption due to NH observed.

It will be seen that the assignment of the frequencies in the four quinones is similar, in that the lower frequency is attributed to the quinonoid-carbonyl group in each case, and the upper frequencies to the *N*-benzoyl or *N*-acetyl group, being respectively lower and higher than the values in the respective simple compounds. Flett [18] has examined analogous benzamido- and acetamido-derivatives of anthraquinone, but was unable to make satisfactory assignments. This was due to his expecting "both the quinone and the other carbonyl bond to be weaker, with lowered characteristic frequencies," and his consequent attempt to assign the lowest frequency in each case to the benzamido- or acetamido-group. The amido-carbonyl bond, however, is only weaker compared to a ketone and, as has been shown above, the sharing of the nucleophobic nitrogen atom with the two carbonyl groups leads to opposite effects in the two cases, compared to the simple quinone or amide. Reassignment of Flett's bands with that of the highest frequency attributed to the benzamido- or acetamido-group gives results consistent among themselves and with the present figures.

A further consideration confirming the respective assignments of the two bands in the present case concerns some intensity measurements. The integrated absorption intensities in chloroform solution of the 1694 and 1633 cm.$^{-1}$ bands of the dibenzoyl compound (V; R = R′ = Bz) are $14{\cdot}6 \times 10^4$ and $8{\cdot}9 \times 10^4$ l. mole^{-1} cm.$^{-2}$ respectively, and of the 1715–1695 doublet and 1634 cm.$^{-1}$ band of the acetyl-benzoyl compound (V; R = Ac, R′ = Bz) $15{\cdot}3 \times 10^4$ and $9{\cdot}8 \times 10^4$ units respectively. Now the amide bands in 2-benzamido-1-naphthyl benzoate, benzanilide, and acetanilide have values of 3·3, 3·2, and $3{\cdot}4 \times 10^4$ units

[18] Flett, *J.*, 1948, 1441.

respectively; the values for the benzamido- and the acetamido-groups in the two compounds above should each be quite close to these figures, so that it is the upper bands which are of about the right intensity for the four amido-carbonyl groups occurring in each case.

Experimental

Methods.—Chlorobenzene and benzoyl peroxide were purified as described by Roitt and Waters.[1] The first oxidations were carried out under a slow stream of purified nitrogen as described by these authors, carbon dioxide evolved being collected in weighed soda-lime tubes. In later experiments these precautions were omitted without affecting either the nature or the yield of the products.

Oxidation of 2-Naphthylamine.—2-Naphthylamine (5 g.), in chlorobenzene (250 ml.), was heated to 80°, and benzoyl peroxide (17 g.) (either as a solid or in chlorobenzene solution) was added at such a rate that the temperature remained at 78—82°. Carbon dioxide (0·09 g.) was evolved and a dark green solid (2·8 g.) separated. The solid, recrystallised from nitrobenzene, yielded *di-(3-benzamido-1 : 4-dihydro-4-oxonaphthylidene)* (I; R = Bz) in dark green needles with a metallic lustre, m. p. 332° (Found: C, 78·1, 78·1; H, 4·7, 4·35; N, 5·2. $C_{34}H_{22}O_4N_2$ requires C, 78·15; H, 4·2; N, 5·4%).

The chlorobenzene solution yielded benzoic acid (11·6 g., 68%) on extraction with aqueous sodium hydrogen carbonate. The solution was dried ($CaCl_2$), the chlorobenzene was removed under reduced pressure, and the red oil was extracted with boiling ether (10 × 150 ml.), to leave a brown amorphous solid (1·2 g.) which was not examined. The combined ether extracts were evaporated to dryness and the residue was chromatographed on alumina (200 g.) (Savory and Moore).

When the alumina column was eluted with light petroleum (b. p. 60—80°), two fractions were obtained which, on evaporation of the solvent, yielded a colourless gum (80 mg.) and a reddish, fluorescent gum (100 mg.) respectively. Elution of the column with benzene–light petroleum (b. p. 60—80°) (1 : 5) yielded a series of fractions, with colours ranging from orange to yellow, which slowly deposited a yellow solid. The combined fractions were evaporated to about 20 ml., more yellow solid separating. The solid, recrystallised from glacial acetic acid, yielded 1 : 2-5 : 6-dibenzophenazine (230 mg.) in pale yellow needles, m. p. and mixed m. p. 284—285° (Found: C, 85·5; H, 5·2; N, 10·1. Calc. for $C_{26}H_{16}N_2$: C, 85·7; H, 4·9; N, 9·9%). The filtrate was evaporated to dryness and the residue was recrystallised twice from ethanol, to yield 2 : 2′-azonaphthalene in red plates, m. p. and mixed m. p. 206—207° (Found: N, 10·0. Calc. for $C_{20}H_{14}N_2$: N, 9·9%).

Elution of the column with benzene–light petroleum (b. p. 60—80°) (1 : 1) yielded a red solution which, on evaporation, gave *2-benzamido-1 : 4-naphthaquinone 4-2′-naphthylimide* (IV; R = NHBz) (850 mg.), separating from ethyl acetate in red needles with a metallic lustre, m. p. 198—199° (Found: C, 80·3, 80·3; H, 4·7, 4·55; N, 7·0, 7·1. $C_{27}H_{18}O_3N_2$ requires C, 80·6; H, 4·5; N, 7·0%). Light absorption (in ethanol): Max., 3020 and 4800 Å (ε 24,000 and 6000).

When the column was eluted with acetone, two fractions were obtained which afforded a blue and a brown powder respectively on evaporation of the solvent. These were not further examined.

(With D. Manson) *Preparation of 3 : 3′-Diamino-4 : 4′-dihydroxy-1 : 1′-dinaphthyl* (II; R = H).—4 : 4′-Dihydroxy-1 : 1′-dinaphthyl (14·3 g.) in water (250 ml.) containing sodium hydroxide (4 g.) and sodium nitrite (7 g.) was cooled to 0° and 10% aqueous sulphuric acid (100 ml.) was added during 30 min., with stirring. After 90 min. the green precipitate (14·6 g.) was centrifuged off and washed with water. A small amount was crystallised from pyridine, to yield *4 : 4′-dihydroxy-3 : 3′-dinitroso-1 : 1′-dinaphthyl* as yellow needles, m. p. >400° (Found: N, 8·3. $C_{20}H_{12}O_4N_2$ requires N, 8·1%).

The crude nitroso-compound (4 g.), in an excess of 2N-sodium hydroxide, was heated to 50° with sodium dithionite (8 g.) until the colour of the nitroso-compound disappeared. The solution was cooled by the addition of ice and neutralised with 2N-hydrochloric acid, and the precipitate was collected, washed with water, and dissolved in hot aqueous 4% hydrochloric acid. The solution was treated with charcoal and an equal volume of concentrated hydrochloric acid was added. The product (3·3 g.) which separated was recrystallised by the addition of concentrated hydrochloric acid to a solution in 4% aqueous hydrochloric acid, to yield *3 : 3′-diamino-4 : 4′-dihydroxy-1 : 1′-dinaphthyl dihydrochloride* (2·6 g.) in silvery-grey plates, m. p. >400° (Found: N, 6·9. $C_{20}H_{18}O_2N_2Cl_2$ requires N, 7·2%). The hydrochloride gave with aqueous ammonia a green colour which could be extracted into benzene.

The *tetrabenzoate* (III; R = Bz) separated from ethyl acetate in needles, m. p. 263—264° (Found: C, 78·5; H, 4·2; N, 3·9. $C_{45}H_{32}O_6N_2$ requires C, 78·7; H, 4·4; N, 3·8%).

Oxidation of 2-*Benzamido*-1-*naphthyl Benzoate.*—This compound (1 g.), in chlorobenzene (10 ml.), was heated at 80° with benzoyl peroxide (1 g.) for 8 hr. The solution was washed with aqueous sodium hydrogen carbonate (3 × 20 ml.), dried ($CaCl_2$), and evaporated to dryness. The residue was chromatographed on alumina, and elution of the column with ether yielded a benzoate, separating from ethyl acetate in needles, m. p. and mixed m. p. 262—263° with the above tetrabenzoate (III; R = Bz). The infrared absorption spectra of the two benzoates were identical.

Reduction of Di-(3-*benzamido*-1 : 4-*dihydro*-4-*oxonaphthylidene*) (I; R = Bz).—The compound (I; R = Bz) (2 g.), zinc dust (2 g.), and acetic acid (780 ml.) were heated together under reflux until the mixture became colourless. The mixture was filtered and immediately diluted with water (1 l.), 3 : 3′-*dibenzamido*-4 : 4′-*dihydroxy*-1 : 1′-*dinaphthyl* (II; R = Bz) (1·9 g.) separating as a blue or pink powder. It was purified by dissolving it in boiling acetic acid containing a little zinc dust and diluting the filtered solution with water; it formed a white powder, m. p. 274—275° (darkening at 250°) (Found: C, 77·6; H, 5·0; N, 5·4. $C_{34}H_{24}O_4N_2$ requires C, 77·85; H, 4·6; N, 5·3%). The phenol yielded a tetrabenzoate, separating from ethyl acetate in needles, m. p. 261—263°, undepressed in admixture with (III; R = Bz), and with identical infrared absorption spectrum.

Hydrolysis of 3 : 3′-*Dibenzamido*-4 : 4′-*dihydroxy*-1 : 1′-*dinaphthyl* (II; R = Bz).—The phenol (2 g.), in methanolic 2N-potassium hydroxide (25 ml.), was heated under reflux for 2 hr., and the solution then diluted with water (100 ml.), acidified with 2N-hydrochloric acid, and filtered. Concentrated hydrochloric acid (100 ml.) was added to the filtrate, 3 : 3′-diamino-4 : 4′-dihydroxy-1 : 1′-dinaphthyl dihydrochloride (950 mg.) separating: it recrystallised, as previously described, in grey plates, m. p. >360° (Found: C, 61·9; H, 5·0; N, 6·8. Calc. for $C_{20}H_{18}O_2N_2Cl_2$: C, 61·7; H, 4·7; N, 7·2%). It formed a tetrabenzoate as needles (from ethyl acetate), m. p. 261—263°, undepressed in admixture with the benzoate (III; R = Bz).

Oxidation of 3 : 3′-*Dibenzamido*-4 : 4′-*dihydroxy*-1 : 1′-*dinaphthyl* (II; R = Bz).—A current of air was drawn through a solution of the phenol (1 g.) in 2N-sodium hydroxide (20 ml.) for 24 hr. The purple powder (800 mg.) which separated was crystallised from nitrobenzene, to yield di-(3-benzamido-1 : 4-dihydro-4-oxonaphthylidene) (I; R = Bz) in dark green needles, m. p. and mixed m. p. 332° (Found: N, 5·7%).

Oxidation of 2-*Benzamido*-1-*naphthol.*—2-Benzamido-1-naphthol (500 mg.), in chlorobenzene (5 ml.), was treated with benzoyl peroxide (1 g.) at 80° as before and the product which separated was recrystallised from nitrobenzene, to yield di-(3-benzamido-1 : 4-dihydro-4-oxonaphthylidene) (I; R = Bz) in dark green needles, m. p. and mixed m. p. 332° (Found: N, 5·3%). This product had an infrared absorption spectrum identical with that of the product from the oxidation of 2-naphthylamine.

Oxidation of 2-*Acetamido*-1-*naphthol.*—2-Acetamido-1-naphthol (500 mg.) was similarly oxidised, to yield *di-*(3-*acetamido*-1 : 4-*dihydro*-4-*oxonaphthylidene*) (I; R = Ac) (220 mg.), separating from nitrobenzene in green plates with a metallic lustre, m. p. 325° (Found: C, 72·5, 72·4; H, 4·7, 4·95; N, 6·8, 7·1. $C_{24}H_{12}O_4N_2$ requires C, 72·35; H, 4·55; N, 7·0%).

Hydrolysis of 2-*Benzamido*-1 : 4-*naphthaquinone* 4-2′-*Naphthylimide* (IV; R = NHBz).—The benzoate (2·5 g.) was heated under reflux with methanolic 2N-potassium hydroxide (50 ml.) for 1 hr. The solution was poured into water, and the red powder collected and crystallised from light petroleum (b. p. 80—100°). 2-Amino-1 : 4-naphthaquinone 4-2′-naphthylimide (IV; R = NH_2) (1·8 g.) formed a red powder, m. p. 136—138° (Found: C, 80·25; H, 4·9; N, 9·3. Calc. for $C_{20}H_{14}ON_2$: C, 80·5; H, 4·7; N, 9·4%). The infrared spectrum of this imide was identical with that of the product which melted at about 135° obtained by Teuber and Jellinek.[15]

When the imide (IV; R = NH_2) (100 mg.), in glacial acetic acid (5 ml.), was heated at 100° with 2-naphthylamine (100 mg.) for 30 min., 2-2′-naphthylamine-1 : 4-naphthaquinone 4-2′-naphthylimide (IV; R = NH·$C_{10}H_7$-β) (120 mg.) separated; from benzene it formed red needles, m. p. 247—248° alone and in admixture with the product from the oxidation of 2-naphthylamine with persulphate [15] (Found: N, 6·5. Calc. for $C_{30}H_{20}ON_2$: N, 6·6%).

The imide (IV; R = NH_2) (50 mg.) was kept overnight with a few drops of acetic anhydride; 2-acetamido-1 : 4-naphthaquinone 4-2′-naphthylimide (IV; R = NHAc) separated: from ethanol it formed purple needles, m. p. 209—210° (Found: N, 8·5. Calc. for $C_{32}H_{16}O_3N_2$: N, 8·2%). Light absorption (in ethanol): Max. 3020 and 4800 Å (ε 25,000 and 6700). The product obtained by Pausacker *et al.*[16] formed purple needles (from ethanol), m. p. 210—212°.

Oxidation of 2-*Acetamidonaphthalene.*—2-Acetamidonaphthalene (10 g.) in chlorobenzene

(250 ml.) was heated at 80° with benzoyl peroxide (10 g.) for 24 hr. Carbon dioxide (0·11 g.) was evolved, and benzoic acid (5·8 g.; 58%) was separated by extraction with aqueous sodium hydrogen carbonate. During this extraction, *3 : 3′-diacetamido-4 : 4′-dibenzoyloxy-1 : 1′-dinaphthyl* (IV; R = Ac) (3·1 g.) separated as a grey solid: from a large volume of ethyl acetate it formed a colourless powder, m. p. 259—260° (Found: C, 74·7; H, 4·8; N, 4·4, 4·6. $C_{38}H_{28}O_6N_2$ requires C, 75·0; H, 4·6; N, 4·6%). Hydrolysis of this product with hot methanolic 2N-potassium hydroxide and subsequent benzoylation yielded the tetrabenzoate (III; R = Bz), m. p. and mixed m. p. 258—259°.

The chlorobenzene solution was diluted with ether (750 ml.), a compound (320 mg.) separating in yellow needles, which recrystallised from chloroform on addition of ether to yield *di-(3-N-acetylbenzamido-1 : 4-dihydro-4-oxonaphthylidene)* (V; R = Ac, R′ = Bz) in bright yellow needles, m. p. 228—229° (decomp.) (Found: C, 75·0; H, 4·3; N, 4·5, 4·55. $C_{38}H_{26}O_6N_2$ requires C, 75·2; H, 4·3; N, 4·6%). When the yellow needles were ground a bright red powder was obtained, which gave, in chloroform, a magenta solution. The chlorobenzene solution was evaporated under reduced pressure to leave a gum which was not investigated further.

Oxidation of 2-Benzamidonaphthalene.—2-Benzamidonaphthalene (5 g.), in chlorobenzene (200 ml.), was heated at 80° with benzoyl peroxide (10 g.) for 36 hr. Carbon dioxide (0·19 g.) was evolved, and benzoic acid (7·3 g., 73%) was extracted from the chlorobenzene solution as before. The solution was then diluted with ether (500 ml.) and kept overnight at 0°. The red plates (210 mg.) which separated recrystallised from chloroform–ether, to yield *di-(3-dibenzoylamino-1 : 4-dihydro-4-oxonaphthylidene)* (V; R = R′ = Bz) as red needles with a golden lustre, m. p. 183—185° (Found: N, 3·9. $C_{48}H_{30}O_6N_2$ requires N, 3·8%), which formed a magenta solution in chloroform.

The chlorobenzene solution was evaporated to dryness under reduced pressure and the residual red oil was chromatographed on alumina. Elution of the column with light petroleum (b. p. 60—80°) and evaporation of the solvent yielded a yellowish oil (120 mg.), which had a bright blue fluorescence in ultraviolet light. The oil was kept for some weeks at 0°, and the crystals which separated were recrystallised from light petroleum (b. p. 60—80°), to yield 2-phenylnaphth-2 : 1-oxazole (15 mg.) in needles, m. p. 120—122°, undepressed on admixture with the product obtained by the method of Worms.[19]

The column was eluted with light petroleum (b. p. 60—80°)–benzene mixtures, with a gradually increasing proportion of benzene. The earlier fractions, on evaporation, yielded unchanged 2-benzamidonaphthalene, separating from benzene in flakes, m. p. and mixed m. p. 162°. The residues from the evaporation of the later fractions were combined and recrystallised three times from benzene, to yield 2 : 2′-dibenzamido-1 : 1′-dinaphthyl (780 mg.) in prismatic needles, m. p. 235—236° (lit.,[20] 235°) (Found: C, 82·95; H, 5·0; N, 5·7. Calc. for $C_{34}H_{22}O_2N_2$: C, 82·9; H, 4·9; N, 5·7%).

The mother-liquors from the recrystallisations of the above dibenzoate were combined and evaporated, and the residue was fractionally crystallised from benzene. From the more soluble fractions, small amounts of two substances were isolated. The first (20 mg.) crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 145—146° (Found: C, 78·0; H, 5·7; N, 4·6%), whilst the second (25 mg.) (possibly 2 : 3′-dibenzamido-4′-benzoyloxy-1 : 1′-dinaphthyl) separated from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 204—205° (Found: C, 80·0; H, 4·9; N, 4·2. Calc. for $C_{41}H_{28}O_4N_2$: C, 80·4; H, 4·6; N, 4·6%).

Elution of the column with ether–acetone (1 : 1) yielded 3 : 3′-dibenzamido-4 : 4′-dibenzoyloxy-1 : 1′-dinaphthyl (III; R = Bz) (520 mg.), separating from ethyl acetate in needles, m. p. and mixed m. p. 263—264° [Found: C, 78·5; H, 4·6; N, 4·0%; *M* (Rast), 697. Calc. for $C_{48}H_{32}O_6N_2$: C, 78·7; H, 4·4; N, 3·8%; *M*, 735]. The infrared absorption of this compound was identical with that of the tetrabenzoate derived from (II; R = Bz).

Elution of the column with acetone yielded an unidentified blue powder (400 mg.).

Reduction of the Compounds (V; R = Ac, R′ = Bz) *and* (V; R = R′ = Bz).—The compounds (100 mg.), in acetic acid (5 ml.), were each heated under reflux with zinc dust (100 mg.) until the colours disappeared. The mixtures were filtered and the filtrates diluted with water (20 ml.). The compound (V; R = Ac, R′ = Bz) yielded a benzoate (50 mg.) as a colourless powder (from ethyl acetate), m. p. and mixed m. p. 258—259° with (III; R = Ac) (Found: N, 4·5%). The infrared spectra of the two compounds were identical. The compound (V; R = R′ = Bz) yielded a tetrabenzoate (60 mg.), separating from ethyl acetate in needles, m. p.

[19] Worms, *Ber.*, 1882, **15**, 1813.
[20] Cumming and Howie, *J.*, 1932, 528.

261—262° undepressed in admixture with (III; R = Bz). The infrared spectra of the two compounds were identical.

Infrared Spectra.—Spectra were measured on a Perkin-Elmer model 112 spectrometer, with a rock-salt prism from 5—15 μ, and one of lithium fluoride in the 3 μ region. Solutions in chloroform were measured in 1 or 3 mm. cells in the 6 μ region, and in 3 or 18 mm. cells at 3 μ. Frequencies quoted should be accurate within ±2 cm.$^{-1}$.

This work was carried out at the suggestion of Professor E. Boyland and we thank him for his interest. Some analyses are by Mr. Oliver of the Microanalytical Laboratory, Imperial College of Science and Technology. This investigation has been supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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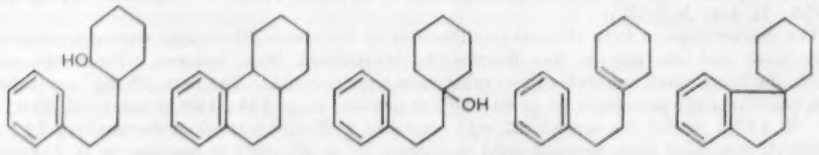
271. *Synthesis of Polycyclic Compounds. Part III.* The Formation of as-Octahydrophenanthrene from the Isomeric 2-Phenethylcyclohexanols.*

By (Mrs.) Manjuli Ray, J. C. Bardhan, and K. C. Bhattacharyya.

A synthesis of 3-phenethyl*cyclo*hexanol is described. This on cyclodehydration, like other isomeric alcohols examined in this connection, affords *as*-octahydrophenanthrene.

It was shown by Bardhan and Sengupta [1] that 2-phenethyl*cyclo*hexanol (I) on treatment with phosphoric anhydride at 140° passed smoothly into *as*-octahydrophenanthrene (II), which could be readily dehydrogenated to phenanthrene. The same octahydrophenanthrene (II) was obtained later by others [2] by the action of sulphuric acid or phosphoric acid on the tertiary alcohol (III). It is now generally recognised, however, that in all such cases the cyclisation proceeds through the olefin (IV), and the resultant product invariably contains also the spiran [3] (V).



(I) (II) (III) (IV) (V)

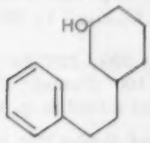
It has been shown [4] that 7-benzyl*iso*menthol [5] undergoes phenanthrene ring closure in the presence of phosphoric anhydride, and the product on dehydrogenation furnishes 3-*iso*propylphenanthrene. As the reaction is somewhat unusual, it seemed of interest to examine the behaviour of 3-phenethyl*cyclo*hexanol (VI) under analogous conditions.

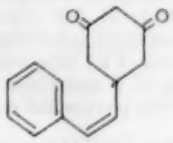
5-Styryl*cyclo*hexane-1 : 3-dione [6] (VII) was allowed to react with phosphoryl chloride,[7] giving 3-chloro-5-styryl*cyclo*hex-2-enone (VIII), which on hydrogenation over colloidal

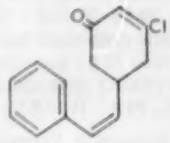
* Part II, *J.*, 1956, 355.

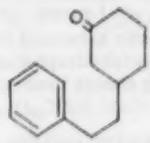
[1] Bardhan and Sengupta, *J.*, 1932, 2520, 2798.
[2] Bogert, *Science*, 1933, **77**, 289; Perlman, Davidson, and Bogert, *J. Org. Chem.*, 1936, **1**, 288; Cook, *Chem. and Ind.*, 1933, **451**; Cook and Hewett, *J.*, 1933, 1098.
[3] Cook, Hewett, and Lawrence, *J.*, 1936, **71**; Cook, Hewett, and Robinson, *J.*, 1939, 168; Levitz, Pulman, and Bogert, *J. Org. Chem.*, 1941, **6**, 105.
[4] Bardhan and Adhya, *J.*, 1956, 260.
[5] Read, Smith, and Hughesdon, *J.*, 1924, **125**, 135; Read and Smith, *J.*, 1923, **123**, 2270.
[6] Vorlander, *Annalen*, 1897, **294**, 132.
[7] Crossley and Pratt, *J.*, 1915, **107**, 173.

palladium [8] furnished 3-phenethyl*cyclo*hexanone (IX). This on further reduction with sodium and moist ether afforded the corresponding alcohol (VI) which, when heated in a vacuum with phosphoric anhydride, gave *as*-octahydrophenanthrene in a good yield, and this on dehydrogenation with selenium at 300—320° was converted almost quantitatively into phenanthrene.


(VI)


(VII)


(VIII)


(IX)

The formation of *as*-octahydrophenanthrene (II) from 3-phenethyl*cyclo*hexanol (VI), which is without precedent, however, presents some interesting analogies with the cyclodehydration [9] of the three isomeric alcohols (X), (XI), and (XII), all of which give 1-methyltetralin in the presence of sulphuric acid or phosphoric acid.

$C_6H_5\cdot[CH_2]_2\cdot CH(OH)\cdot CH_2\cdot CH_3$ (X) $C_6H_5\cdot[CH_2]_3\cdot CH(OH)\cdot CH_3$ (XI) $C_6H_5\cdot[CH_2]_4\cdot CH_2\cdot OH$ (XII)

The physical properties of the *as*-octahydrophenanthrene described above are in good agreement with those previously recorded [3] for this hydrocarbon. From its method of formation it seems highly probable that it is free from contamination with the isomeric spiran (V), although this has not been rigidly established.

Experimental

5-Styrylcyclohexane-1 : 3-dione [6] (VII).—This substance has been prepared before, but the following procedure is much more expeditious. A solution of sodium (23 g.) in absolute ethanol (375 ml.) was heated with ethyl malonate (160 g.) and cinnamylideneacetone (b. p. 155—156°/4 mm.) (172 g.) on the water-bath for 6 hr. It was treated with water (400 ml.), and ethanol was removed on the water-bath. Aqueous potassium hydroxide (100 g. in 100 ml.) was then added, and the liquid made up to 1250 ml. by water and boiled in an open flask for 25 min. It was filtered, acidified, and boiled as before until no more carbon dioxide was evolved. On cooling, the crystalline product (206 g.) was collected, washed with water, and purified from ethanol (charcoal). It had m. p. 183—184° (lit.,[6] 186°).

3-Chloro-5-styrylcyclohex-2-enone (VIII).—The diketone (VII) (32·1 g.), suspended in dry chloroform (75 ml.), was refluxed with phosphorus trichloride (6·5 ml.) on the water-bath for 3 hr. The chloroform was distilled off, the residue decomposed with ice-water, and the resulting emulsion extracted with ether. The ethereal solution was washed with 4% aqueous sodium hydroxide, then with water, dried, and distilled. The *chloro-ketone* (VIII) (15 g.) distilled almost constantly (b. p. 180—182°/4 mm.) (Found : Cl, 15·7. $C_{14}H_{13}OCl$ requires Cl, 15·3%).

3-Phenethylcyclohexanone (IX).—A solution of the chloro-ketone (VIII) (13 g.) in ethanol (50 ml.) was hydrogenated at 30° in the presence of gum arabic (0·1 g.), dissolved in water (5 ml.), and palladium chloride (0·1 g.) until hydrogen (4216 ml. Calc. : 4156 ml.) was absorbed (3 hr.). After filtration, the solution was evaporated to half its bulk, diluted with water, and extracted with ether. The ethereal solution was washed, dried, and distilled. The *ketone* (10·3 g.), having a faint but characteristic smell, had b. p. 152—153°/6 mm. (Found : C, 83·1; H, 8·8. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%). The *semicarbazone* crystallised from aqueous ethanol as plates, m. p. 181—182° (Found : C, 69·6; H, 8·3. $C_{15}H_{21}ON_3$ requires C, 69·5; H, 8·2%).

3-Phenethylcyclohexanol (VI).—A mixture of the above ketone (12 g.), ether (60 ml.), and water (50 ml.) was stirred mechanically, and sodium (12 g.) was introduced gradually with occasional cooling in ice-water. When all the sodium had dissolved (4 hr.), the ethereal layer was separated, the alkaline solution was extracted with ether, and the combined ethereal solutions were washed with water, dried (K_2CO_3), and evaporated. *3-Phenethylcyclohexanol* (10 g.) had b. p. 152°/4 mm. (Found : C, 82·5; H, 9·9. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%).

[8] Skita and Franck, *Ber.*, 1911, **44**, 2862.
[9] Bogert *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 185, 959; 1935, **57**, 151.

The 3 : 5-*dinitrobenzoate*, prepared in pyridine, crystallised from ethanol in needles, m. p. 121—122° (Found : C, 63·5; H, 5·7. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·5%).

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydrophenanthrene* (II).—The foregoing alcohol (3 g.) was heated with phosphoric anhydride (7 g.) for 0·5 hr. at 135—140°/4 mm. The temperature was then allowed to rise slowly and between 160° and 170° a colourless oil (2 g.) distilled. This was dried, and distilled over sodium, giving pure *as*-octahydrophenanthrene, b. p. 128°/6 mm., d_4^{20} 0·99736, n_D^{20} 1·54859, $[R_L]_D$ 59·28 (Found : C, 90·4; H, 9·8. Calc. for $C_{14}H_{18}$: C, 90·3; H, 9·7%), fully saturated towards potassium permanganate and bromine.

The octahydrophenanthrene (2 g.) and selenium (4 g.) were heated at 300—320° for 20 hr., giving an almost theoretical yield of phenanthrene, m. p. and mixed m. p. 100° (Found : C, 94·2; H, 5·5. Calc. for $C_{14}H_{10}$: C, 94·4; H, 5·6%). The picrate had m. p. and mixed m. p. 145°.

UNIVERSITY COLLEGE OF SCIENCE & TECHNOLOGY, CALCUTTA. [*Received, October 31st*, 1955.]

272. *Synthesis of Polycyclic Compounds. Part IV.* Substituted 3-Alkylphenanthrenes.*

By J. C. BARDHAN, R. N. ADHYA, and K. C. BHATTACHARYYA.

The synthesis described in Part I * has been extended to the preparation of 3-methyl-, 1 : 3-, 2 : 3-, and 3 : 8-dimethyl-, 1 : 2 : 3-, 2 : 3 : 8-, and 1 : 3 : 8-trimethyl-, and 1 : 2 : 3 : 8-tetramethyl-phenanthrene.

IN Part I * a new synthesis of alkylphenanthrenes was described starting from ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate, $CO_2Et{\cdot}[CH_2]_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}COMe$. In continuation of this work γ-ethoxycarbonyl-β-methylbutyryl chloride has been condensed with ethyl sodioacetoacetate giving ethyl 2-methyl-4 : 6-dioxoheptane-1 : 5-dicarboxylate (I), which reacted with phenethyl bromide in presence of sodium ethoxide to yield ethyl 2-methyl-4-oxo-7-phenylheptane-1 : 5-dicarboxylate (II; R′ = H). This was cyclised with concentrated sulphuric acid at 0°, and the product on hydrolysis furnished γ-(2-carboxy-3 : 4-dihydro-1-naphthyl)-β-methylbutyric acid (III; R′ = H). The ethyl ester of this acid was dehydrogenated with sulphur, to yield ethyl γ-(2-ethoxycarbonyl-1-naphthyl)-β-methylbutyrate (IV; R = Et, R′ = H), which on condensation by means of sodium and then hydrolysis gave 1 : 2 : 3 : 4-tetrahydro-3-methyl-1-oxophenanthrene (V; R′ = R″ = H). Similarly, the ester (IV; R = Et, R′ = H) on treatment with sodium followed by methylation and hydrolysis afforded 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethyl-1-oxophenanthrene (V; R′ = H, R″ = Me). The cyclic ketones (V; R′ = R″ = H) and (V; R′ = H, R″ = Me) on Clemmensen reduction and dehydrogenation, in the usual way, gave 3-methyl-[1] and 2 : 3-dimethyl-phenanthrene [2] respectively.

1 : 2 : 3 : 4-Tetrahydro-3-methyl-1-oxophenanthrene (V; R′ = R″ = H) was condensed with methylmagnesium iodide in ethereal solution, the resultant alcohol dehydrated with 100% formic acid, and the unsaturated product dehydrogenated to 1 : 3-dimethylphenanthrene [3] by selenium. 1 : 2 : 3-Trimethylphenanthrene was prepared in a similar manner from 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethyl-1-oxophenanthrene (V; R′ = H, R″ = Me). The constants for this hydrocarbon and its derivatives are, however, slightly lower than those previously recorded.[4]

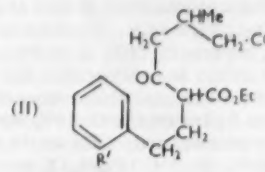
In other experiments 2-*o*-tolylethyl bromide was condensed with the ester (I), yielding ethyl 2-methyl-4-oxo-7-*o*-tolylheptane-1 : 5-dicarboxylate (II; R′ = Me). This was converted by way of ethyl γ-(2-ethoxycarbonyl-5-methyl-1-naphthyl)-β-methylbutyrate (IV; R = Et, R′ = Me), 1 : 2 : 3 : 4-tetrahydro-3 : 8-dimethyl-1-oxophenanthrene (V; R′ = Me, R″ = H), and 1 : 2 : 3 : 4-tetrahydro-2 : 3 : 8-trimethyl-1-oxophenanthrene (V; R′ = R″ = Me), into 1 : 6-dimethyl-[2a] and 1 : 6 : 7-trimethyl-phenanthrene [5] by methods

* Parts I, II, III, *J.*, 1956, 350, 355, and preceding paper.

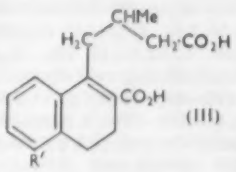
[1] (*a*) Pschorr, *Ber.*, 1906, **39**, 3111; (*b*) Haworth, *J.*, 1932, 1132.
[2] (*a*) Haworth *et al.*, *J.*, 1934, 458; (*b*) Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1508.
[3] Bogert and Stamatoff, *Rec. Trav. chim.*, 1933, **52**, 584.
[4] Fieser and Daudt, *J. Amer. Chem. Soc.*, 1941, **63**, 782.
[5] Haworth and Bolam, *J.*, 1932, 2248.

developed in an analogous case. The properties and derivatives of these hydrocarbons agree with those recorded previously.

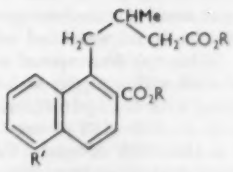
$CO_2Et{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO{\cdot}CH(CO_2Et){\cdot}COMe$ (I)



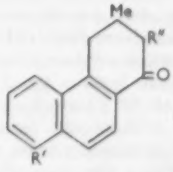
(II)



(III)



(IV)



(V)

The action of an excess of methylmagnesium iodide on an ethereal solution of 1 : 2 : 3 : 4-tetrahydro-3 : 8-dimethyl-1-oxophenanthrene (V; R′ = Me, R″ = H), followed by dehydration and dehydrogenation, gave 1 : 3 : 8-trimethylphenanthrene,[6] which has been prepared recently by an alternative route. In an analogous manner 1 : 2 : 3 : 4-tetrahydro-2 : 3 : 8-trimethyl-1-oxophenanthrene (V; R′ = R″ = Me) yielded 1 : 2 : 3 : 8-tetramethylphenanthrene, characterised as its picrate.

Experimental

γ-Ethoxycarbonyl-β-methylbutyric Acid.—Ethyl crotonate (34·2 g.) and ethyl malonate (48 g.) were refluxed with a solution of sodium (1·2 g.) in absolute ethanol (60 ml.) for 6 hr., yielding ethyl α-ethoxycarbonyl-β-methylglutarate [7] (73 g.), b. p. 136—138°/3 mm. This was converted into β-methylglutaric anhydride, b. p. 145—148°/3 mm., m. p. 41°, and γ-ethoxycarbonyl-β-methylbutyric acid, b. p. 141—143°/3 mm., in the usual way.[8]

Ethyl 2-Methyl-4 : 6-dioxoheptane-1 : 5-dicarboxylate (I).—To powdered sodium (10 g.) under ether (450 ml.), ethyl acetoacetate (56·4 ml.) in ether (125 ml.) was added slowly with cooling and occasional swirling. The suspension of the sodio-salt was cooled in a freezing mixture, and a solution of γ-ethoxycarbonyl-β-methylbutyryl chloride (from the acid, 75·3 g., and thionyl chloride, 33 ml.) in ether (150 ml.) was added dropwise with shaking. After remaining in the cold overnight the mixture was gently refluxed for 1 hr., and the product worked up in the usual manner. On repeated distillation the *diketo-ester* (86 g.) had b. p. 155—156°/3 mm. (Found: C, 58·5; H, 7·8. $C_{14}H_{22}O_6$ requires C, 58·7; H, 7·7%). It gives a crimson colour with ethanolic ferric chloride and probably contains a little of the isomeric *O*-acyl ester.

Ethyl 2-Methyl-4-oxo-7-phenylheptane-1 : 5-dicarboxylate (II; R′ = H).—The above diketo-ester (28·6 g.) was added with shaking to an ice-cold solution of sodium (2·3 g.) in absolute ethanol (40 ml.), and next morning the clear solution was mixed with phenethyl bromide (18·5 g.) and heated at 90° for 18 hr. On cooling, ice and dilute sulphuric acid were added, and the organic layer was collected in ether. The ethereal solution was washed, dried, and distilled. The substituted *keto-ester* (II; R′ = H) formed a pale yellow oil (14·7 g.), b. p. 191—193°/3 mm. (Found: C, 68·8; H, 8·1. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·0%). It gives a reddish-violet colour with ethanolic ferric chloride.

γ-(2-Carboxy-3 : 4-dihydro-1-naphthyl)-β-methylbutyric Acid (III; R′ = H).—The ester (II; R′ = H) (5 g.) was added dropwise with vigorous stirring during 5 min. to concentrated sulphuric

[6] King and King, *J.*, 1953, **4158**; 1954, 1373.
[7] Michael and Ross, *J. Amer. Chem. Soc.*, 1930, **52**, 4598; Hunsdiecker, *Ber.*, 1942, **75**, 1197; Auwers *et al.*, *Ber.*, 1891, **24**, 2887.
[8] Darbishire and Thorpe, *J.*, 1905, **87**, 1716; Stallberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **25**, *A*, No. 10; Linstead *et al.*, *J.*, 1950, 3332.

acid (30 ml.) cooled in a freezing mixture. The brownish liquid was stirred in the cold for 3 hr. more and then poured on powdered ice, and the mixture repeatedly extracted with ether. The ethereal solution was washed, dried, and evaporated. The residual oil was hydrolysed with a solution of potassium hydroxide (3 g.) in water (3 ml.) and ethanol (30 ml.) and worked up in the usual way. The *acid* separated from aqueous acetic acid (charcoal) (2·5 g.) as prisms, m. p. 166° (Found : C, 70·3; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·5%). The *ethyl ester* had b. p. 188—190°/3 mm. (Found : C, 72·5; H, 7·9. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·8%).

γ-(2-Carboxy-1-naphthyl)-β-methylbutyric Acid (IV; R = R′ = H).—The preceding ester (8 g.) was heated with sulphur (0·8 g.) at 240—260° for 2 hr., and the product on distillation gave an oil (7·8 g.), b. p. 200—205°/3 mm. This was hydrolysed with 10% ethanolic potassium hydroxide, and the crude acid (7·5 g.) purified by esterification. The *ethyl ester* (IV; R = Et, R′ = H), b. p. 202—203°/3 mm. (Found : C, 73·2; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·3%), on hydrolysis gave the *acid*, prisms, m. p. 169° (from benzene; charcoal) (Found : C, 70·9; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

1 : 2 : 3 : 4-*Tetrahydro-3-methyl-1-oxophenanthrene* (V; R′ = R″ = H).—The ester (IV; R = Et, R′ = H) (9·8 g.), benzene (25 ml.), and finely divided sodium (0·8 g.) were heated on the steam-bath until the sodium dissolved and the liquid was filled with the crystalline sodio-derivative of the condensation product (3 hr.). This was decomposed with ice and dilute hydrochloric acid, and the benzene layer isolated, washed with aqueous sodium carbonate, dried, and evaporated. The crude oil (10 g.) was hydrolysed with hot hydrochloric acid (20 ml.) and acetic acid (40 ml.) for 10 hr. The cyclic *ketone*, b. p. 182—183°/3 mm., solidified. From light petroleum (b. p. 60—80°) it formed prisms, m. p. 102—103° (Found : C, 85·9; H, 6·7. $C_{15}H_{14}O$ requires C, 85·7; H, 6·6%). The *semicarbazone* crystallises from ethanol in plates, m. p. 262° (Found : C, 71·5; H, 6·4. $C_{16}H_{17}ON_3$ requires C, 71·9; H, 6·3%).

1 : 2 : 3 : 4-*Tetrahydro-2 : 3-dimethyl-1-oxophenanthrene* (V; R′ = H, R″ = Me).—The solid sodio-salt produced by the Dieckmann condensation of the ester (IV; R = Et, R′ = H) (10 g.), finely divided sodium (0·9 g.), and benzene (25 ml.) was cooled in ice, methyl iodide (6 ml.) added, and the reaction allowed to proceed at room temperature. The mixture was then refluxed for 20 hr., and the product (11 g.), isolated in the usual way, was hydrolysed with hydrochloric acid (22 ml.) and acetic acid (44 ml.) as described above. The *oxo-compound* (V; R′ = H, R″ = Me) on distillation afforded an oil (3·8 g.), b. p. 182—187°/3 mm., which solidified and afforded colourless needles, m. p. 99°, from light petroleum (b. p. 40—60°) (Found : C, 85·6; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%). The *semicarbazone* separated from ethanol in prisms, m. p. 253° (decomp.) (Found : C, 72·1; H, 6·7. $C_{17}H_{19}ON_3$ requires C, 72·6; H, 6·7%).

3-Methylphenanthrene.—The ketone (V; R′ = R″ = H) (1 g.) was reduced by boiling with amalgamated zinc (10 g.), concentrated hydrochloric acid (15 ml.), and water (3 ml.) for 24 hr. On distillation over sodium 1 : 2 : 3 : 4-*tetrahydro-3-methylphenanthrene* formed a pale yellow oil (0·5 g.), b. p. 160—163°/3 mm. (Found : C, 91·5; H, 8·2. $C_{15}H_{16}$ requires C, 91·8; H, 8·2%). The product was dehydrogenated with selenium (1 g.) at 310—320° for 24 hr. The hydrocarbon was isolated and distilled over sodium, and recrystallised from ethanol in needles, m. p. 60—61° (Found : C, 93·8; H, 6·2. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·3%). The picrate crystallises from ethanol in needles, m. p. 136—137° (Found : C, 59·5; H, 3·6. Calc. for $C_{15}H_{12}.C_6H_3O_7N_3$: C, 59·8; H, 3·5%). Pschorr [15] gives m. p.s 65° and 141°, and Haworth [15] 62—63° and 137—138° respectively.

2 : 3-*Dimethylphenanthrene.*—The cyclic ketone (V; R′ = H, R″ = Me) was reduced by Clemmensen's method, and the product distilled over sodium. 1 : 2 : 3 : 4-*Tetrahydro-2 : 3-dimethylphenanthrene* had b. p. 165°/3 mm. (Found : C, 91·3; H, 8·7. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%). 2 : 3-Dimethylphenanthrene, obtained on dehydrogenation with selenium, crystallised from ethanol in prisms, m. p. 78—79° (Found : C, 93·4; H, 6·9. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). The picrate separated in orange needles (from ethanol), m. p. 145—146° (Found : C, 60·2; H, 4·0. Calc. for $C_{16}H_{14}.C_6H_3O_7N_3$: C, 60·7; H, 3·9%). Fieser and Hershberg [16] give m. p.s 78—78·5° and 146—147°, and Haworth *et al.*[23] give 65—66° and 138—140° respectively.

1 : 3-*Dimethylphenanthrene.*—The ketone (V; R′ = R″ = H) (1·2 g.), in dry ether (30 ml.), was added slowly at room temperature to ethereal methylmagnesium iodide (from magnesium, 0·6 g., methyl iodide, 2 ml., and ether, 30 ml.). The mixture was gently boiled for 4 hr., and decomposed with ice and dilute sulphuric acid, the ethereal layer was separated and dried (K_2CO_3), and the solvent removed. The alcohol (1·2 g.) was heated with 100% formic acid (3 ml.) for 0·5 hr., and the product (1 g.) on dehydrogenation with selenium afforded 1 : 3-dimethylphenanthrene, which crystallised from ethanol in prisms, m. p. 75—76° (lit.,[3] 76—77°)

(Found : C, 93·0; H, 6·7%). The picrate crystallised from ethanol in orange needles, m. p. 154—155° (lit.,[3] 154—155°) (Found : C, 60·3; H, 4·0%).

1 : 2 : 3-*Trimethylphenanthrene*.—This was prepared by the action of methylmagnesium iodide on 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethyl-1-oxophenanthrene as described above. It had b. p. 180°/3 mm., but solidified; it recrystallised from ethanol as plates, m. p. 58—59° (Found : C, 93·1; H, 7·3. Calc. for $C_{17}H_{16}$: C, 92·8; H, 7·2%). The picrate formed bright orange needles (from ethanol), m. p. 181° (Found : C, 61·2; H, 4·3. Calc. for $C_{17}H_{16}.C_6H_3O_7N_3$: C, 61·5; H, 4·2%). The trinitrobenzene derivative formed yellow needles (from ethanol), m. p. 192°. Fieser and Daudt [4] record m. p.s 63·8—64·8°, 187—188°, and 200·7—201·5°, respectively.

Ethyl 2-Methyl-4-oxo-7-o-tolylheptane-1 : 5-dicarboxylate (II; R′ = Me).—This was prepared as described above for an analogous case, from sodium (2·3 g.), absolute ethanol (40 ml.), the ester (I) (28·6 g.), and 2-*o*-tolylethyl bromide (19·9 g.). The *keto-ester* (II; R′ = Me) (14 g.), b. p. 206—208°/3 mm. (Found : C, 69·4; H, 8·4. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%), gave a positive ferric reaction.

γ-(*2-Carboxy-5-methyl-3 : 4-dihydro-1-naphthyl*)-β-*methylbutyric Acid* (III; R′ = Me).—The preceding keto-ester was cyclised with concentrated sulphuric acid as described above and the product hydrolysed in the usual way. The *acid* (III; R′ = Me) was purified by repeated crystallisation from dilute acetic acid (charcoal), and formed colourless prisms, m. p. 212° (Found : C, 70·9; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%). The *diethyl ester* distills at 200—203°/3 mm. (Found : C, 73·1; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·1%).

γ-(*2-Carboxy-5-methyl-1-naphthyl*)-β-*methylbutyric Acid* (IV; R = H, R′ = Me).—The above diethyl ester was heated with sulphur in the usual way and the product on hydrolysis gave the *acid* (IV; R = H, R′ = Me), which recrystallised from acetic acid as needles, m. p. 202° (Found : C, 71·3; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The corresponding *diethyl ester* (IV; R = Et, R′ = Me) had b. p. 210—212°/3 mm. (Found : C, 73·6; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%).

1 : 2 : 3 : 4-*Tetrahydro-3 : 8-dimethyl-1-oxophenanthrene* (V; R′ = Me, R = H).—This was prepared according to Dieckmann's procedure followed by hydrolysis of the product with hydrochloric–acetic acid. The *ketone* (b. p. 187—189°/3 mm.) readily solidified and from benzene–light petroleum (b. p. 60—80°) formed prisms, m. p. 130° (Found : C, 85·9; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%). The *semicarbazone* separated from aqueous ethanol in prisms, m. p. 275—276° (Found : C, 72·2; H, 6·8. $C_{17}H_{19}ON_3$ requires C, 72·6; H, 6·7%).

1 : 2 : 3 : 4-*Tetrahydro-2 : 3 : 8-trimethyl-1-oxophenanthrene* (V; R′ = R″ = Me).—The product of the sodium condensation described above was methylated and hydrolysed in the usual way. The *ketone* (V; R′ = R″ = Me) (b. p. 192—194°/3 mm.) solidified and crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 133° (Found : C, 85·9; H, 7·6. $C_{17}H_{18}O$ requires C, 85·7; H, 7·5%). The *semicarbazone* separated from ethanol in prisms, m. p. 225° (Found : C, 73·0; H, 7·1. $C_{18}H_{21}ON_3$ requires C, 73·2; H, 7·1%).

1 : 6-*Dimethylphenanthrene*.—The cyclic ketone (V; R′ = Me, R″ = H) was reduced by Clemmensen's method, and the product dehydrogenated with selenium. 1 : 6-Dimethylphenanthrene crystallised from methanol in plates, m. p. 87—88° (lit.,[3a] 87—88°) (Found : C, 93·4; H, 6·9%), and the picrate in orange needles, m. p. 139—140° (lit.,[3a] 134°) (Found : C, 60·3; H, 4·0%).

1 : 6 : 7-*Trimethylphenanthrene*.—This was prepared in an analogous manner from the ketone (V; R′ = R″ = Me). It crystallised from absolute ethanol in plates, m. p. 124° (lit.,[5] 123—124°) (Found : C, 92·9; H, 7·3%). The picrate, orange needles from ethanol, had m. p. 165—166° (lit.,[5] 165—166°) (Found : C, 61·1; H, 4·3%).

1 : 3 : 8-*Trimethylphenanthrene*.—The ketone (V; R′ = Me, R″ = H) (1·5 g.) was treated with methylmagnesium iodide from magnesium (0·7 g.), methyl iodide (2·5 ml.), and ether (40 ml.), and the mixture boiled for 4 hr. The alcohol was isolated, dehydrated, and dehydrogenated as described above. The pure hydrocarbon separated from absolute ethanol (charcoal) in needles, m. p. 116° (lit.,[6] 116°) (Found : C, 92·9; H, 7·3%). The picrate crystallised from ethanol in orange needles, m. p. 174° (lit.,[6] 174—175°) (Found : C, 61·2; H, 4·2%), and the trinitrobenzene derivative in bright yellow needles, m. p. 188° (lit.,[6] 188°).

1 : 2 : 3 : 8-*Tetramethylphenanthrene*, prepared similarly from the ketone (V; R′ = R″ = Me), crystallised from absolute ethanol in needles, m. p. 96—97° (Found : C, 92·6; H, 7·7. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%), and the *picrate* from ethanol in orange-red needles, m. p. 193° (Found : C, 62·0; H, 4·5. $C_{18}H_{18}.C_6H_3O_7N_3$ requires C, 62·2; H, 4·5%).

UNIVERSITY COLLEGE OF SCIENCE & TECHNOLOGY, CALCUTTA. [*Received, October 31st*, 1955.]

273. *Vibrational Frequencies and Thermodynamic Properties of Fluoro-, Chloro-, Bromo-, and Iodo-benzene.*

By D. H. Whiffen.

An assignment of all the fundamental vibration frequencies of fluorobenzene, chlorobenzene, bromobenzene, and iodobenzene is given in Table 1, and the spectroscopic thermodynamic properties are given in Table 3.

The majority of the Raman shifts of the halogeno-benzenes have been assigned by Kohlrausch and Wittik [1] and the infrared and Raman spectra of fluorobenzene have been discussed by Smith, Ferguson, Hudson, and Nielsen.[2] The infrared spectra have been measured by Lecomte [3] who makes a partial assignment, and also at the National Bureau of Standards.[4, 5] The assignment suggested in Table 1 follows these authors to a considerable extent and in it values are suggested for all the thirty fundamental frequencies of each compound, so that the thermodynamic properties can be calculated.

Assignment

In the first column of Table 1 is given a code letter designation for the vibration in accordance with the approximate mode diagrams of Randle and Whiffen [6] which is reprinted in the Figure; the next column indicates the symmetry class, and this is followed by the chosen frequencies. The molecules are isomorphous and belong to the C_{2v} symmetry group, and each possesses 11 A_1 class fundamental frequencies, 10 B_1, 3 A_2, and 6 B_2 frequencies, but it is more convenient to discuss the values in terms of the approximate description of the normal modes, rather than to take each symmetry class separately. The more certain assignments will be considered first and the three less well-established frequencies thereafter in sections (9), (10), and (11).

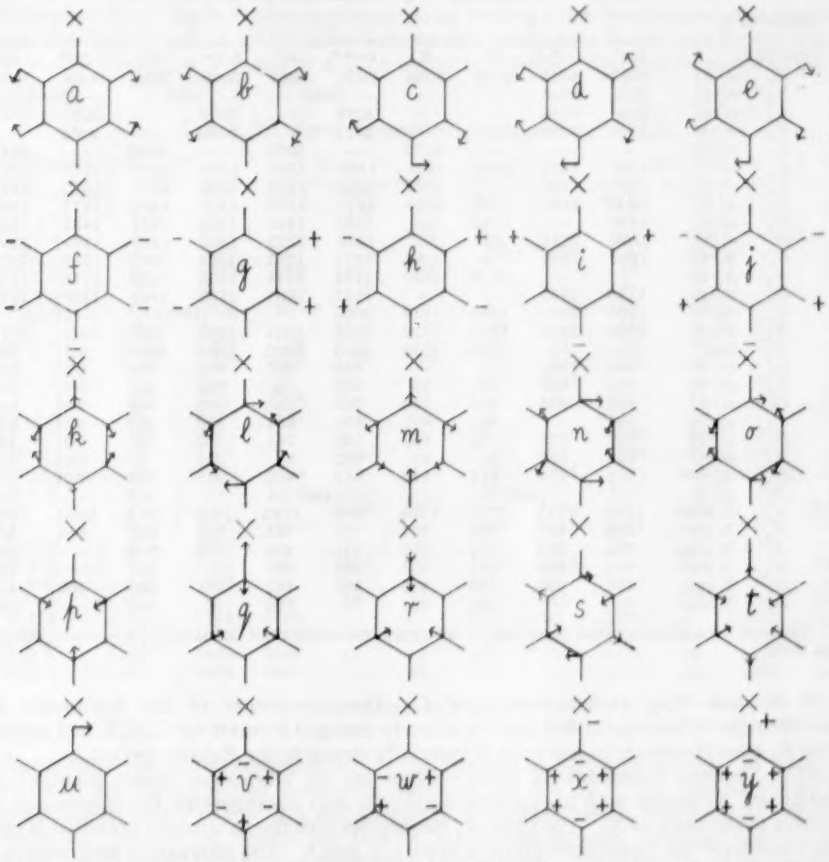
(1) C–H *Stretchings* (*Abbreviation* νC–H).—There are five essentially C–H stretching modes for each compound, whose frequencies must lie in the range 2950—3120 cm.$^{-1}$ by analogy with other aromatic C–H frequencies.[7] But the summation frequencies k + m, k + n, l + m, and l + n are also in this range, and strong Fermi interactions are likely to occur, as in benzene itself.[8] Consequently an extensive investigation with high resolution is likely to be required to establish these frequencies and the suggestions of Table 1 are extremely tentative. Fortunately the thermodynamic properties are not very sensitive to the exact values chosen.

(2) C–C *Stretchings* (νC–C).— There are 2 A_1 and 3 B_1 modes which are essentially C–C stretchings. It is known that one of each class lies near 1600 cm.$^{-1}$, being derived from the degenerate E_{2g} benzene frequency near 1597 cm.$^{-1}$. It is only in the Raman spectrum of fluorobenzene that the two frequencies, k and l, are clearly resolved. The A_1 frequencies related to the E_{1u} frequency of benzene at 1480 cm.$^{-1}$ must be those of the strong infrared absorption of row m and the corresponding B_1 frequencies must be those of row n. These lie some 30 cm.$^{-1}$ lower, since this motion involves some admixture of C–X deformation. For the third B_1 frequency see section (10) below.

(3) *In-plane* C–H *Deformations* (βC–H).—There are two A_1 vibrations whose frequencies are almost unchanged from those of benzene at 1178 and 1033 cm.$^{-1}$ and certainly correspond to rows a and b; these frequencies appear plainly in the Raman spectra. Two of the B_1 frequencies will resemble those of the in-plane C–H deformations of monodeuterobenzene which [9] are at 1158 and 1075 cm.$^{-1}$, and rows c and d list the values. The

[1] Kohlrausch and Wittik, *Monatsh.*, 1943, **74**, 1.
[2] Smith, Ferguson, Hudson, and Nielsen, *J. Chem. Phys.*, 1953, **21**, 1475.
[3] Lecomte, *J. Phys. Radium*, 1937, **8**, 489.
[4] Amer. Petroleum Inst., Project **44**. Infrared spectra contributed by the National Bureau of Standards.
[5] Plyler, *Discuss. Faraday Soc.*, 1950, **9**, 100.
[6] Randle and Whiffen, Molecular Spectroscopy. Conference held by the Institute of Petroleum, London, 1954.
[7] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954.
[8] Herzfeld, Ingold, and Poole, *J.*, 1946, 316.
[9] Bailey, Gordon, Hale, Herzfeld, Ingold, and Poole, *J.*, 1946, 299.

d frequencies are obscured by q in bromo- and iodo-benzene, but there can be little doubt that they are at about 1068 cm.$^{-1}$ as in chlorobenzene and in other monosubstituted benzenes.[6] Indeed in the infrared spectrum [10] of iodobenzene in CS_2 the 1060 cm.$^{-1}$ band is asymmetric in shape and consistent with a medium-intensity band at 1068 cm.$^{-1}$. The frequency 1156 cm.$^{-1}$ for fluorobenzene is assigned to modes in both the A_1 and the B_1 class. There seems to be no reason for the expected B_1 frequency, c, not to lie at this frequency: the A_1 mode, a, would be depressed from its normal value 1175 cm.$^{-1}$ by the adjacent X-sensitive mode, q, at 1220 cm.$^{-1}$ and by the A_1 class energy level $\nu + y$ at 1183 cm.$^{-1}$. The intensity of the 1156 cm.$^{-1}$ Raman line in fluorobenzene, which is greater than those of row c, adds weight to this suggestion. For the remaining B_1 frequencies see section (11).



[Reprinted, by permission, from Randle and Whiffen, "Molecular Spectroscopy," Institute of Petroleum, London, 1955, pp. 111—123.]

(4) *Ring Frequencies.*—The extremely strong, polarized, Raman lines of row p certainly arise from the A_1 trigonal ring breathings in which the substituent scarcely moves.

(5) *Out-of-plane* C–H *Deformations* (γC–H).—The lowest of the three B_2 C–H out-of-plane deformation frequencies, row *f*, is known to give very strong infrared absorption. The lower of the two A_2 frequencies is almost unchanged from the corresponding benzene

[10] Randle and Whiffen, *Trans. Faraday Society*, 1956, **52**, 9.

vibration at 849 cm.$^{-1}$ and is indicated by the medium-intensity Raman shifts of row g. Row i corresponds to medium infrared absorption and accounts for a second B_2 mode; the frequencies are slightly below the corresponding deuterobenzene value[9] of 922 cm.$^{-1}$. Rows h and j are less evident in the fundamental spectra, but the evidence of the summation tones from 1700 to 2000 cm.$^{-1}$ indicates that these have been correctly chosen, as has been discussed in detail elsewhere.[11]

(6) *Out-of-plane Ring Deformations* (ϕC–C).—The strong infrared bands of row v clearly correspond to the B_2 ring deformation in agreement with the calculated value[12] of 698 cm.$^{-1}$ and the deuterobenzene value[9] also of 698 cm.$^{-1}$. The A_2 frequencies are discussed in section (9).

TABLE 1. *Assignment of fundamentals of* C_6H_5X.

	Nature of X		F				Cl		Br		I	
	Spectrum		I–r[3]	I–r[4, 5]	R[2]	R[1]	I–r[4, 5]	R[2]	I–r[4, 5]	R[2]	I–r[4, 5]	R[2]
z_1	A_1	νC–H	3067	3065	3072	3084	3071	3067	3069	3065	3064	3070
z_2	A_1	νC–H	3053	3049	—	—	— (3050)	—	— (3050)	—	— (3050)	—
z_3	A_1	νC–H	3040	3036	—	—	3029	—	3029	—	3031	—
z_4	B_1	νC–H	3100	3095	—	—	3071	—	3069	—	3064	—
z_5	B_1	νC–H	—	—	—	3072	—	3052	—	3056	—	3048
k	A_1	νC–C	1597	1592	1602	1603	1580	1583	1580	1577	1575	1571
l	B_1	νC–C	1597	1592	—	1596	1580	1583	1580	1577	1575	1571
m	A_1	νC–C	1499	1492	1496	1496	1477	1479	1473	1472	1473	1469
n	B_1	νC–C	1460	—	1457	xx	1445	1443	1445	1441	1435	1436
o	B_1	νC–C	1326	1324	xx	xx	1326	1322	1323	1319	1321	1318
e	B_1	βC–H	1290	1282	xx	1295	1271	1263	1264	1263	1261	1255
a	A_1	βC–H	—	—	1156	1157	1174	1174	1175	1176	1178	1175
c	B_1	βC–H	1156	1155	—	—	1157	1157	1159	1158	1159	1156
d	B_1	βC–H	1066	1065	1065	1068	1068	—	— (1068)	—	— (1068)	—
b	A_1	βC–H	1020	1020	1021	1024	1026	1024	1021	1020	1015	1017
p	A_1	ring	—	—	1009	1010	1003	1002	1001	1001	998	999
j	B_2	γC–H	980	982	—	—	985	987	988	990	987	988
h	A_2	γC–H	955	955	xx	xx	965	xx	963	xx	963	xx
i	B_2	γC–H	896	896	896	900	902	xx	903	906	904	xx
g	A_2	γC–H	831	—	829	831	830	832	832	832	835	838
f	B_2	γC–H	752	752	754	759	740	741	735	737	730	731
v	B_2	ϕC–C	685	682	687	xx	682	xx	681	—	684	xx
s	B_1	αC–C–C	615	615	613	612	616	615	615	614	613	613
w	A_2	ϕC–C	—	— (400)	—	—	— (400)	xx	—	409	—	398
q	A_1	X sens.	1220	1219	1217	1218	1085	1083	1070	1071	1060	1060
r	A_1	X sens.	806	806	806	807	701	702	669	673	654	654
t	A_1	X sens.	520	519	519	519	415	418	314	315	—	266
u	B_1	X sens.	405	406	407	407	297	297	—	254	—	220
y	B_2	X sens.	501	499	499	496	467	467	458	460	448	450
x	B_2	X sens.	—	—	242	241	—	196	—	181	—	166

Symbols: xx frequency not observed, — spectrum obscured or not measured, () frequency inferred, see text.

(7) *In-plane Ring Deformation* (αC–C–C).—One component of the degenerate E_{2g} class vibration of benzene at 606 cm.$^{-1}$ is scarcely changed in mode for C_6H_5X and appears as the B_1 class frequency in row s; it is especially strong in the Raman spectra.

(8) *X-Sensitive Vibrations* (X *sens.*).—There are six vibrational modes in which the substituent, X, moves with appreciable amplitude and consequently the frequencies are sensitive to the mass of X. The three A_1 frequencies give rise to strongly polarized Raman lines [1] and have the frequencies given in rows q, r, and t. The alternative assignments by Plyler [5] are unacceptable as they place polarized Raman line frequencies in the B_2 class. Modes q, r, and t all involve appreciable C–X stretching and it would not be justified to call any particular row the C–X stretching frequencies. In contrast only one B_1 mode is sensitive to the mass of X and may be called the C–X in-plane deformation mode. The values given in row u agree with Garg's approximate calculations.[13] The two sensitive B_2 frequencies for each molecule are given in rows y and x; the fluorobenzene frequencies

[11] Whiffen, *Spectrochim. Acta*, 1955, **7**, 253.
[12] Whiffen, discussion, see ref. 6.
[13] Garg, *Current Sci.*, 1953, **22**, 298.

at 499 and 241 cm.$^{-1}$ agree with the approximate calculations [12] which gave 490 and 247 cm.$^{-1}$. The heavier halogens have rather lower frequencies, as is to be expected. Also the lowest B_2 frequency, row x, lies below the lowest B_1, row u, which is consistent with a lower out-of-plane than in-plane deformation force constant; for aromatic C–H links the values[14] are 0·286 and 0·864 × 10^5 dynes/cm. respectively.

The discussion above has accounted for twenty-seven of the fundamentals in each case and discussion of the remaining modes has been postponed to this point since the evidence involves summation frequencies of the more certain modes already given.

(9) *Out-of-plane* A_2 *Ring Deformation.*—The missing A_2 ring deformation frequency, row w, cannot, from its symmetry class, involve any motion of the substituent. Departures from the corresponding E_{2u} benzene frequency at 405 cm.$^{-1}$ are therefore likely to be small since the C–C twisting force constant remains essentially unchanged. Kohlrausch and Wittik [1] adduce experimental evidence for frequencies near 400 cm.$^{-1}$ from the Raman spectra, while Table 2 shows that summation bands may be explained as 2w, v + w, w + g, w + i, and w + j, by use of this value. The last three are important

TABLE 2. *Some summation frequencies of* C_6H_5X.

Nature of X		F				Cl		Br		I	
Spectrum		I–r[2]	I–r[4,5]	R[2]	R[1]	I–r[4,5]	R[2]	I–r[4,5]	R[2]	I–r[4,5]	R[2]
t − x	B_2	—	—	277	274	—	—	—	—	—	—
t + x	B_2	—	—	—	—	—	—	xx	502	—	—
2x	A_1	—	—	—	—	390 ?	382	—	365	—	321
t + u	B_1	925	925	xx	xx	—	—	545	xx	—	xx
x + y	A_1	—	—	—	—	—	xx	628	—	—	—
x + w	B_1	653	651	—	—	xx	—	xx	—	—	—
2w	A_1	—	—	—	—	810	—	812	—	790	—
m–s, e–w	B_1, B_2	875	874	xx	xx	860	xx	862	xx	862	xx
2y, f + x	A_1, A_1	996	995	997	997	936	934	912	xx	—	xx
r + t	A_1	—	—	—	—	1123	1121	—	—	919	xx
v + w	B_1	1105	1104	xx	xx	—	—	1095	xx	1095	xx
v + y	A_1	1190	1185	xx	xx	—	—	1133	xx	1125	xx
f + y	A_1	1255	—	xx	xx	1212	xx	1196	xx	1186	—
w + g	A_1	1235	—	—	—	1234	xx	1233	xx	1231	xx
w + i	B_1	1302	1299	xx	1301	1299	1294	1299	xx	1302	xx
i + y	A_1	1397	1393	—	—	1374	—	1362	—	1351	—
2v	A_1	—	—	1369	1370	—	1372	—	1365	—	1361
j + w	A_1	1397	1393	—	—	1389	1399	1385	—	1379	—
v + g	B_1	1531	—	xx	xx	—	xx	—	xx	1522	xx
s + p	B_1	1624	—	1623	1626	1626	1614	—	1614	—	1619
i + f	A_1	1652	—	—	—	1647	—	1639	—	1636	—
2g	A_1	—	—	xx	xx	—	xx	—	1667	—	1666
g + i	B_1	1714	1709	—	—	1736	xx	1736	xx	1739	xx
g + h	A_1	1778	1773	1789	xx	1795	xx	1795	xx	1798	xx
i + h	B_1	1855	1855	xx	xx	1873	xx	1873	xx	1872	xx
h + j	B_1	1939	1938	—	xx	1949	xx	1949	xx	1949	xx

Symbols as in Table 1.

evidence since the corresponding bands in the infrared spectrum of benzene[8] at 1248 and 1381 cm.$^{-1}$ are interpreted as summation bands of the 405 cm.$^{-1}$ E_{2u} frequency with the benzene equivalents [11] of rows g, i, and j, namely, the degenerate E_{1g} frequency at 849 cm.$^{-1}$ and the B_{2g} frequency at 985 cm.$^{-1}$. This evidence seems stronger than that for the value 330 cm.$^{-1}$ in fluorobenzene.[2] The summation bands thought to require the value 330 cm.$^{-1}$ have alternative explanations, namely: 565 (d − u = 561, d − w = 565); 653 (x + w = 642, x + u = 647); 955 (A_2 fundamental); 1190 (v + y = 1186); 1789 (2i = 1792); 3373 (m + n + u = 3360 cm.$^{-1}$).

(10) B_1 C–C *Stretching Frequency.*—If Mair and Hornig [15,16] are followed in placing the

[14] Whiffen, *Phil. Trans.*, 1955, **248**, 131.
[15] Mair and Hornig, *J. Chem. Phys.*, 1949, **17**, 1236.
[16] Additional argument in favour of the new assignment was given by F. A. Miller at the Ohio State Meeting on Molecular Spectroscopy, 1955; *J. Chem. Phys.*, in the press.

B_{2u} frequency of benzene at 1310 cm.$^{-1}$ the missing B_1 C–C stretching frequencies of the substituted benzenes must have similar values. The infrared spectra show two possible bands for each compound near 1320 cm.$^{-1}$, row o, and near 1300 cm.$^{-1}$. The Raman evidence [1] is in favour of the former set which corresponds to Raman frequencies in three of the spectra; w + i is an acceptable attribution to the 1300 cm.$^{-1}$ frequencies. The fluorobenzene frequency at 1326 cm.$^{-1}$ might be r + t = 1326 cm.$^{-1}$, but no explanation other than B_1 fundamental could be found for the other frequencies of row o.

(11) B_1 C–H *In-plane Deformation.*—There remain the highest B_1 C–H deformations which are likely to be only a little lower than 1292 cm.$^{-1}$, the value [9] for deuterobenzene, and the values in row e are suggested. Possible alternative candidates nearer 1230 cm.$^{-1}$ are more probably w + g. The suggestion [2] that the missing frequency is 875 cm.$^{-1}$ in fluorobenzene would imply that this compound has C–H deformation force constants which are very different from those in benzene, which is improbable. The summation frequencies thought to involve 875 cm.$^{-1}$ can all be otherwise explained: 1190 (v + y = 1186); 1485 (j + y = 1480); 1676 (t + a = 1676, t + c = 1676); 1939 (h + j = 1936); 2375 (a + q = 2377, c + q = 2377). The 875 cm.$^{-1}$ frequency itself is less satisfactorily explained, but the frequencies m − s = 881, e − w = 890, e − u = 884 cm.$^{-1}$, are all available. Nor is 1236 cm.$^{-1}$ essential as a fundamental,[2] for the frequencies that might involve this value can be explained as: 1735 (g + i = 1727, q + t = 1740); 2491 (n + d = 2480); 2846 (z_4 − y = 2848 cm.$^{-1}$). 1236 cm.$^{-1}$ itself is probably w + g = 1231 cm.$^{-1}$, which involves transition to an A_1 level, and the infrared band could derive part of its intensity by interaction with the 1220 cm.$^{-1}$ fundamental.

The last two B_1 assignments are also supported by calculations for deuterobenzene using force constants [14] appropriate to the Mair and Hornig assignment for benzene. The calculations lead to frequencies of 1314 and 1291 cm.$^{-1}$, but the normal co-ordinates show that there is considerable mixing of the C–C stretching and C–H deformation co-ordinates. w + i is a third B_1 energy level in this frequency region, and the description of the three frequencies as C–C stretching fundamental, w + i summation, and C–H deformation fundamental is a gross simplification of the true state of affairs.

The more important summation frequencies and their interpretation are given in Table 2. Some of the assignments have already been discussed and other comments are to be found in the references cited.[1, 2, 11] The remaining points are not of sufficient importance or certainty to warrant detailed discussion, but Table 2 does show that the frequencies are capable of at least one explanation in terms of the chosen fundamentals.

It can be seen that the assignment of any one halogenobenzene has been made more certain by considering together the analogous vibrations of all four compounds. This approach could readily be extended to other monosubstituted benzenes. If a general rather than a particular substituent were considered the result would be essentially Table 1 of reference 6. This Table is in agreement with the present interpretations except in a few minor particulars: (i) Line 2 contains a misprint in the class designation which should read B_1 for the s mode. (ii) The frequency near 962 cm.$^{-1}$ is [11] that of the A_2 mode h and that near 982 cm.$^{-1}$ belongs to the B_2 mode j. (iii) The highest B_1 C–H deformation mode, e, seems to be near 1270 cm.$^{-1}$ rather than 1240 cm.$^{-1}$ which is the value for the summation tone w + g. (iv) The last row with frequencies near 1663 cm.$^{-1}$ is more probably [11] f + i than either o or s + b.

It is interesting that the frequencies of the halogenobenzenes are in many cases essentially unchanged in passing from fluoro- to iodo-benzene despite the change of electronegativity [17] from 4·0 to 2·5. This implies that the force constants governing the carbon and hydrogen motions are also unchanged. Apart from the specifically X-sensitive motions, the greatest frequency deviation seems to be 22 cm.$^{-1}$ in row f which is analogous to the modes discussed in relation to Hammett's σ values by Bellamy.[18] Rows k, l, m, and n are also more sensitive than the average, but they correspond to ring frequencies which are more likely to be mass-sensitive than the hydrogen frequencies.

[17] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1945.
[18] Bellamy, *J.*, 1955, 2818.

Thermodynamic Properties

These fundamental frequencies were used to calculate the vibrational contributions to the thermodynamic properties; an average value between the infrared and Raman frequencies was used if these differed. For determining the rotational contributions accurate moments of inertia are available for fluoro-[19] and chloro-benzene.[20] For bromo- and iodo-benzene the distances[21] 1·86 ± 0·03 Å for C–Br and 2·08 ± 0·04 Å for C–I were assumed and the moments of inertia calculated with the aid of the additional assumption that the moment of inertia of benzene itself could be assumed to be $148{\cdot}0 \times 10^{-40}$ about an axis in the plane of the ring. This is the value found by Erlandsson[19,20] for the smallest moment of chloro- and fluoro-benzene and is consistent with the Raman value for benzene obtained by Stoicheff.[22] The limits of error given correspond to ±0·02 in $(H^\circ_0 - G^\circ)/RT$ and S°/R. The total contributions are given in Table 3 which relates to 1 mole of perfect gas at 1 atmosphere. Spin contributions are excluded, except through the intervention of the symmetry number, as are isotopic mixing terms. The usual high-temperature and harmonic oscillator approximations were made, and the computation was shortened by the use of the tables quoted by Pitzer;[23] values of the fundamental constants were taken from the same source.

Calorimetric values for the liquid-state entropies and specific heats have been given by Stull.[24] From these, gas-state entropies can be obtained by using the latent-heat data suggested by Jones and Bowden[25] and interpolating the vapour pressures from Stull's data.[26] If gas imperfections are neglected, the resulting entropies at 25° c are those given in

Table 3. *Thermodynamic properties.*

Temp. (K)	200°	273·16°	298·16°	300°	400°	500°	600°	800°	1000°
				Fluorobenzene					
$(H^\circ_0 - G^\circ)/RT$	27·58	29·31	29·87	29·91	32·02	34·04	35·98	39·67	43·08
$(H^\circ - H^\circ_0)/RT$	5·09	6·13	6·52	6·55	8·23	9·90	11·67	14·18	16·37
S°/R	32·67	35·44	36·39	36·46	40·25	43·94	47·65	53·85	59·45
C°_p/R	7·61	10·37	11·33	11·40	15·03	18·05	20·45	23·91	26·26
				Chlorobenzene					
$(H^\circ_0 - G^\circ)/RT$	28·38	30·22	30·81	30·85	33·07	35·18	37·19	40·97	44·44
$(H^\circ - H^\circ_0)/RT$	5·40	6·49	6·90	6·93	8·61	10·28	11·83	14·50	16·67
S°/R	33·78	36·71	37·70	37·78	41·68	45·45	49·02	55·47	61·11
C°_p/R	8·13	10·84	11·79	11·86	15·41	18·36	20·71	24·10	26·41
				Bromobenzene					
$(H^\circ_0 - G^\circ)/RT$	29·50	31·40	32·01	32·05	34·34	36·49	38·53	42·36	45·87
$(H^\circ - H^\circ_0)/RT$	5·61	6·71	7·12	7·15	8·82	10·47	12·01	14·65	16·80
S°/R	35·11	38·12	39·13	39·20	43·16	46·96	50·54	57·01	62·67
C°_p/R	8·43	11·07	11·99	12·06	15·56	18·47	20·79	24·15	26·44
				Iodobenzene					
$(H^\circ_0 - G^\circ)/RT$	30·31	32·28	32·90	32·94	35·27	37·45	39·52	43·39	46·92
$(H^\circ - H^\circ_0)RT$	5·79	6·89	7·29	7·32	8·98	10·61	12·13	14·76	16·89
S°/R	36·10	39·16	40·18	40·26	44·25	48·07	51·66	58·14	63·80
C°_p/R	8·62	11·21	12·12	12·19	15·65	18·55	20·85	24·19	26·47

Table 4. *Standard vapour entropy*, S° (e.u.) *at* 298·16° K.

	C_6H_5F	C_6H_5Cl	C_6H_5Br	C_6H_5I
Calorimetric	69·9	71·8	74·5	74·7
Spectroscopic	72·32	74·92	77·76	79·85

Table 4, where they are compared with the spectroscopic values at the same temperature. The calorimetric values are consistently lower by 2—5 e.u. This difference is rather

[19] Erlandsson, *Arkiv Fys.*, 1953, **7**, 189.
[20] *Idem, ibid.*, 1954, **8**, 341.
[21] Schoppe, *Z. phys. Chem.*, 1936, **34**, *B*, 461.
[22] Stoicheff, *J. Chem. Phys.*, 1953, **21**, 1410.
[23] Pitzer, "Quantum Chemistry," Constable, London, 1953.
[24] Stull, *J. Amer. Chem. Soc.*, 1937, **59**, 2726.
[25] Jones and Bowden, *Phil. Mag.*, 1946, **37**, 480.
[26] Stull, *Ind. Eng. Chem.*, 1947, **39**, 517.

larger than Stull's[24] estimate of 3% as his error, though some allowance must be made for errors in the vapour pressures and latent heats. But the main uncertainty is possibly in the reliability of Stull's extrapolation for the entropy change from 0° to 91° K, and a direct determination of specific heats below 91° K would be desirable. It is not easy to estimate errors in the spectroscopic values, which are uncertain owing to neglect of anharmonicity and the use of liquid-state frequencies; also there is uncertainty of about 10 cm.$^{-1}$ in the exact values of row w of Table 1. Providing there is no major error of assignment, the properties in Table 3 are probably correct within $\pm 0{\cdot}2$ in the quantities listed.

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274. *Synthesis of Di*[ar-^{14}C]*benzoyl Peroxide from* [^{14}C]*Benzene.*

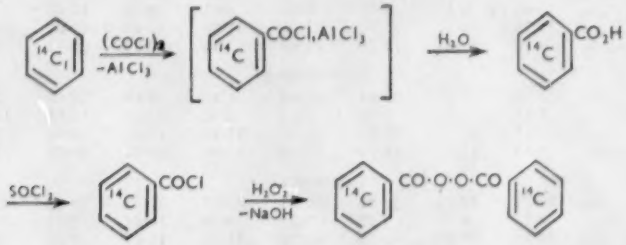
By G. AYREY and C. G. MOORE.

Di[*ar*-^{14}C]benzoyl peroxide has been synthesised on the 1 mmole scale from [^{14}C]benzene *via* [*ar*-^{14}C]benzoic acid and [*ar*-^{14}C]benzoyl chloride.

Trial syntheses with inactive compounds indicated an overall yield of 40—50%, while radiochemical assay of the active peroxide indicated an overall yield of 35%.

RECENT studies in these laboratories of the polymerisation of vinylic monomers in the presence of natural rubber have demonstrated the importance of the initiating catalyst on the reaction, *viz.*, benzoyl peroxide leads to extensive rubber-polymer interaction ("grafting"), but azo*iso*butyronitrile, while initiating polymerisation, does not cause significant interaction.[1] A mechanistic study of the "grafting" process is being undertaken using [^{14}C]-labelled initiators, and the present paper describes the synthesis of di[*ar*-^{14}C]benzoyl peroxide from [^{14}C]benzene.

The synthetic route chosen is shown in the following scheme :



Staudinger's method[2] was used to convert benzene into benzoyl chloride, which was hydrolysed, without isolation, to benzoic acid. Trial syntheses on the 1 mmole scale gave yields of 80—95% of substantially pure benzoic acid, and in the final radioactive synthesis a 95% yield of [*ar*-^{14}C]benzoic acid was obtained. This was converted into the peroxide by reaction as shown.[3] Experimental conditions influence the yield of peroxide considerably. An excess of sodium hydroxide considerably reduces the yield, probably by hydrolysis of the peroxide before it could be isolated, while addition of a trace of oleic acid as emulsifying agent increases the yield.[4] Pure inactive benzoyl chloride gave yields of peroxide up to 85%, but when the benzoyl chloride was prepared from benzoic acid the yield of peroxide was lowered to 50—55% based on the acid, probably owing to partial

[1] Merrett, *Trans. Faraday Soc.*, 1954, **50**, 759.
[2] Staudinger, *Ber.*, 1908, **41**, 3558.
[3] Vanino and Herzer, *Arch. Pharm.*, 1915, **253**, 426; Gambarjan, *Ber.*, 1909, **42**, 4004.
[4] Oosterhuis, Dutch P., 51,098/1941.

loss of benzoyl chloride during the removal of unchanged thionyl chloride and the resultant inability to assess the correct amount of sodium hydroxide to be used. Rigorous removal of thionyl chloride was imperative for the successful synthesis of the peroxide since small amounts remaining are readily converted by the sodium hydroxide into sulphite which then is oxidised by the hydrogen peroxide, thus resulting in loss of both reagents.

The di[*ar*-^{14}C]benzoyl peroxide was diluted with pure inactive peroxide, equilibrated in chloroform, and precipitated with methanol to give di[*ar*-^{14}C]benzoyl peroxide (1). A second sample (2) of the peroxide was obtained from the mother-liquors of the first sample, and its radiochemical purity demonstrated by two dilution experiments involving recrystallisations from different solvents to give samples (3) and (4). Table 1 indicates

TABLE 1. *Radiochemical assay of di*[ar-^{14}C]*benzoyl peroxide.*

Sample	1	2	3	4
Observed activity (counts/min./mmole)	$2{\cdot}75 \times 10^7$	$6{\cdot}45 \times 10^6$	$1{\cdot}34 \times 10^5$	$5{\cdot}88 \times 10^4$
Calculated activity * (counts/min./mmole)	$2{\cdot}82 \times 10^7$	—	$1{\cdot}38 \times 10^5$	$5{\cdot}97 \times 10^4$

* Based on the specific activity of sample (2) and the known dilution factors.

the radiochemical purities. From the specific activities and the counting efficiency of the Geiger–Müller tube (determined by radioassay of compounds of known specific activity) it was calculated that the radiochemical yield of the peroxide was 35% based on [^{14}C]benzene.

EXPERIMENTAL

Inactive Materials.—Commercial benzoyl peroxide was recrystallised twice from ether, then once from acetone, precipitated twice from chloroform with methanol, and dried *in vacuo*, to

FIG. 1.

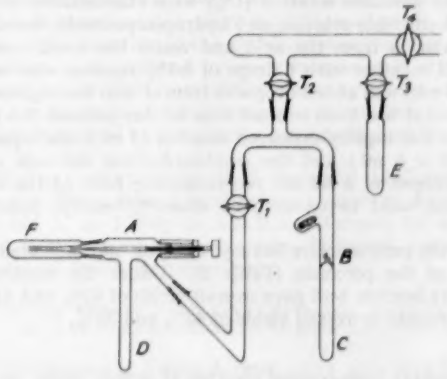
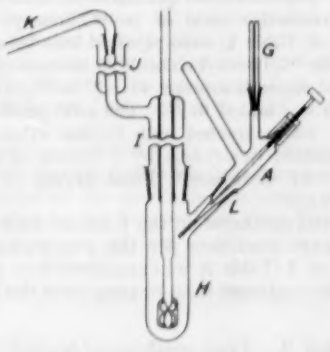


FIG. 2.



give pure peroxide (Found : C, 69·4; H, 4·2. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·2%). Analysis by Nozaki's method[5] indicated a purity of 99·7%. Reagents and solvents were purified by standard procedures or were of " AnalaR " grade.

[ar-^{14}C]*Benzoic Acid.*—[^{14}C]Benzene in carbon disulphide was introduced into the micro-dropping funnel *A* (see Fig. 1) by the following procedure. With the entire apparatus evacuated, tap T_1 open, and T_2 and T_4 closed, the seal at *B* was broken, and [^{14}C]benzene (0·078 g., 1 mmole; 0·5 mc) was distilled from tube *C* into tube *D* cooled in liquid oxygen. Taps T_2 and T_3 were then opened and carbon disulphide (4·0 ml.) was distilled from *E* into *D*. T_1 was then closed, the dropping funnel was detached from the vacuum manifold, and the contents of *D* were melted and mixed by gentle shaking. Air was introduced through T_1 into the dropping funnel which was attached to the apparatus shown in Fig. 2 at *L*. The long capillary tube *G* prevented loss by evaporation.

[5] Nozaki, *Ind. Eng. Chem. Anal.*, 1946, **18**, 583.

Simultaneously with the above, aluminium chloride (1·34 g., 10 mmole) and carbon disulphide (2·0 ml.) were placed in the tube *H* (Fig. 2). The apparatus also comprised a precision-ground stirrer *I*, a solid carbon dioxide condenser *J* and an " Anhydrone " drying tube *K*. Oxalyl chloride (1·15 g., 9 mmole) in carbon disulphide (5·0 ml.) was added to vessel *H* with stirring and the whole kept at 25° for 30—40 min., during which gentle effervescence occurred (evolution of carbon monoxide as carbonyl chloride was formed). The contents of *H* were then cooled to 0°, and with vigorous stirring the [^{14}C]benzene solution was introduced from *A* at the rate of one drop per 12—15 sec. (total time of addition, 75 min.). The syringe *A* was washed with further carbon disulphide (2 ml.), and the washings were added to *H*. Tube *K* was then replaced by a stopper, *I* was sealed at the top with thick " Silicone " grease, and the volatile material removed *via L* at 15 mm. into a trap cooled in liquid oxygen. Water (8·0 ml.) was slowly added to the solid complex in *H* at 0°, and the mixture then refluxed for 15—30 min. On cooling, benzoic acid crystallised. Next morning, tube *H* was transferred to an extraction apparatus described elsewhere.[6] The aqueous mixture was extracted with ether (5, 3, and 2 ml.), the combined ether extracts were extracted with 10% aqueous sodium hydroxide (3, 2, and 1 ml.), and the alkaline extracts washed with ether (5 ml.) and then acidified with concentrated hydrochloric acid (1 ml.). The [*ar*-^{14}C]benzoic acid was extracted with ether (3 × 5 ml.), the resulting solution evaporated to dryness, and the acid dried over phosphorus pentoxide at 200 mm. (yield, 0·116 g., 95%). In trial syntheses the benzoic acid, m. p. and mixed m. p. 120—121°, was obtained in yields of 80, 85, and 95% (Found: C, 68·2; H, 5·0; ash 0·8%; equiv., 124. Calc. for $C_7H_6O_2$: C, 68·9; H, 5·0%; equiv., 122).

[ar-^{14}C]*Benzoyl Chloride.*—A mixture of [*ar*-^{14}C]benzoic acid (0·116 g., 0·95 mmole) and thionyl chloride (2 ml., 27·5 mmole) was refluxed for 4 hr. in a 25 ml. pear-shaped flask protected with an " Anhydrone " drying tube. A fine capillary nitrogen-leak was then fitted to the flask and the excess of thionyl chloride distilled off into a trap cooled in liquid oxygen, the final traces being removed at room temp./15 mm. during 5—10 min. Benzene (0·75 ml.) was then added to the [*ar*-^{14}C]benzoyl chloride and distilled off as for the thionyl chloride.

Di[ar-^{14}C]*benzoyl Peroxide.*—The apparatus used is shown in Fig. 2. Sodium hydroxide solution (2·4%) and " AnalaR " hydrogen peroxide solution (1%) were standardised before use. The calculated quantities of sodium hydroxide solution and hydrogen peroxide, based on a quantitative yield of [*ar*-^{14}C]benzoyl chloride from the acid and under the conditions of expt. 3, Table 2, were pipetted into tube *H* together with 6 drops of 0·7% aqueous oleic acid. The [*ar*-^{14}C]benzoyl chloride in acetone (0·5 ml.) was added dropwise from *A* into the vigorously stirred aqueous solution at −2° to 0°; vessel *A* was then washed with further acetone (0·5 ml.) which was added to *H*. The solid product was rapidly dissolved in ether (5 ml.), the aqueous layer was extracted with further ether (2 × 5 ml.) and the combined ether extracts were evaporated to dryness by a stream of nitrogen in a 50 ml. recrystallising flask of the type described elsewhere.[6] Final drying of the solid *in vacuo* gave di[*ar*-^{14}C]benzoyl peroxide (0·068 g.).

Trial syntheses on the 1 mmole scale with pure inactive benzoyl chloride had indicated the optimum conditions for the preparation of the peroxide (Table 2). Under the conditions of expt. 3 (Table 2) trial syntheses from pure benzoic acid gave overall yields of 52% and 54%; similar syntheses from benzene gave the peroxide in overall yields of 43% and 58%.

TABLE 2. *Trial syntheses of benzoyl peroxide from benzoyl chloride* (1 *mmole scale*) *at* 0°.

Expt.	Molar ratio NaOH (aq.) : BzCl	Molar ratio H_2O_2 (aq.) : BzCl	Yield † (%)
1	1·0	0·5	57
2 *	1·0	0·5	83
3 *	1·0	0·75	89
4 *	1·5	0·5	67

* 6 Drops of 0·7% aq. oleic acid present. † Determined iodometrically.[5]

Dilution of Di[ar-^{14}C]*benzoyl Peroxide.*—The above peroxide was transferred with chloroform (5 ml.) *via* the filter disc into a second crystallising flask containing pure inactive peroxide (1·505 g.). After complete dissolution and thorough equilibration the peroxide was precipitated at 0° with methanol (5 ml.), and the solid peroxide separated, redissolved in chloroform (4 ml.),

[6] Ayrey, Moore, and Watson, *J. Polymer Sci.*, 1956, **19**, 1.

and reprecipitated at 0° with methanol (4 ml.) to give di[*ar*^{14}C]benzoyl peroxide (1) (0·978 g.), which when assayed as described below had an activity of $1{\cdot}97 \times 10^6$ counts/min./mmole of CO_2.

The combined mother-liquors were evaporated to dryness at room temp./15 mm. and the peroxide, together with inactive peroxide (2·004 g.), dissolved in chloroform and precipitated three times with methanol as described above to give sample (2) (1·48 g.) having an activity of $4{\cdot}61 \times 10^6$ counts/min./mmole of CO_2. The radiochemical purity of sample (2) was demonstrated by two further dilution experiments. First, sample (2) (33·07 mg.) and inactive peroxide (1·511 g.) were equilibrated in warm acetone (4·5 ml.) and crystallised at 0°; the solid peroxide was twice precipitated with methanol from chloroform to give sample (3) (0·694 g.) having an activity of $9{\cdot}56 \times 10^5$ counts/min./mmole of CO_2. Secondly, sample (2) (14·19 mg.) and inactive peroxide (1·518 g.) were equilibrated in, and crystallised from, ether, then precipitated as above from chloroform solution, to give sample (4) (0·684 g.) having an activity of $4{\cdot}20 \times 10^5$ counts/min./mmole of CO_2. The observed specific activities of samples (1), (3), and (4) (Table 1) are in good agreement with those calculated from the observed specific activity of sample (2) and the known dilution factors.

Assay of Samples for [^{14}C].—The samples were oxidised to water and $^{14}CO_2$ by the standard dry microcombustion technique, the water was removed in an "Anhydrone" drying tube and a trap cooled in ethanol–carbon dioxide, and the $^{14}CO_2$ collected in a trap[7] cooled in liquid oxygen. Sample weights were such as to give a maximum of 1·25 mmole of carbon dioxide. The $^{14}CO_2$ was diluted, if necessary, with inactive carbon dioxide and then transferred, together with carbon disulphide, to the Geiger–Müller counter of the type described by Audric and Long[8] (Bevington, Guzman, and Melville's technique[9]). The counter was placed in a lead shield ($1\frac{1}{2}$" thick), and the plateau determined for all samples; the plateaux usually had a slope of $<0{\cdot}05\%$ per volt, and their length exceeded 100 volts. Counting was done at 75 v. from the beginning of the plateau and sufficient counts were taken to give a standard error of less than $\pm 1\%$. Count rates recorded have been corrected for lost counts due to an imposed paralysis time of 1 msec. in the scaler, background (*ca.* 20 counts/min.), and dilution. Memory effects in the combustion apparatus, the vacuum manifold, and the counter were shown to be negligible. In all combustions the yield of $^{14}CO_2$ was $100 \pm 1{\cdot}0\%$, indicating that the carbon dioxide is truly representative of the carbon content of the compound burnt. The performance of the counter was determined by using samples of $^{14}CO_2$ of different specific activity, and was satisfactory up to 5000 counts/min. (linearity of the plot of count rate against relative activity). The count rates of $^{14}CO_2$ samples derived from [^{14}C]poly(methyl methacrylate) and barium [^{14}C]carbonate of known specific activity showed the efficiency of the counter to be 45%.

The authors thank Mr. B. N. Audric of the Chemical Research Laboratory, Teddington, and Dr. J. C. Bevington of Birmingham University for advice on the radiochemical assay of $^{14}CO_2$, and Mr. L. A. Kilbey of A.E.R.E., Harwell, for services to the electronic equipment. This work forms part of the programme of research undertaken by the Board of the British Rubber Producers' Research Association.

British Rubber Producers' Research Association,
48, Tewin Road, Welwyn Garden City, Herts. [*Received, November 28th*, 1955.]

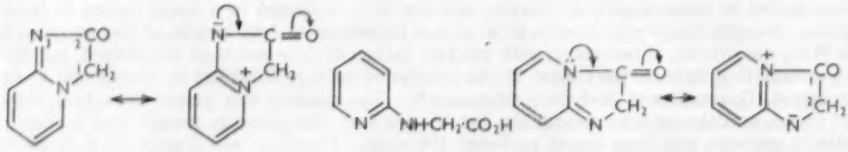
[7] Buchanan and Nakao, *J. Amer. Chem. Soc.*, 1952, **74**, 2389.
[8] Audric and Long, Report No. CRL/AE 51, Chemical Research Laboratory, Teddington.
[9] Bevington, Guzman, and Melville, *Proc. Roy. Soc.*, 1954, *A*, **221**, 437.

275. *The Colour of Organic Compounds. Part VIII.* A Comparison of Isomeric Dyes from 3 : 7a-Diazaindan-1-one and -2-one.*

By Edward B. Knott.

N-2-Pyridylaminoacetic acid (II) has been cyclized by phosphorus trichloride to 3 : 7*a*-diazaindan-1-one (III). The latter contains a nucleophilic methylene-carbon atom and has been converted into methin and dimethin dyes. The absorptions of these dyes have been compared with those of isomeric dyes derived from 3 : 7*a*-diazaindan-2-one (I), and the differences explained on the basis of the author's colour rule.[1]

Dyes derived from 3 : 7*a*-diazaindan-2-one (I) have been described [2] and it was of interest to compare their spectral properties with those of isomers derived from 3 : 7*a*-diazaindan-1-one (III). The required precursor of the amide (III) is *N*-2-pyridylaminoacetic acid (II), which has been obtained by acid hydrolysis of the readily accessible *N*-2-pyridylaminoacetonitrile.[3]

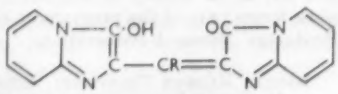


(I) (Ia) (II) (III) (IIIa)

Whereas the diazaindan-2-one (I) is usually obtained by heating 1 : 2-dihydro-2-imino-1-pyridylacetic acid [the isomer of (II)] with mineral acid,[4] the acid (II) is less readily cyclized. With phosphorus trichloride at 95—100°, however, practically quantitative yields of the hydrochloride of the amide (III) are obtained. The hydrochloride is deliquescent and unstable towards water or alcohols. Conversion into dyes is, therefore, best carried out in a solvent such as pyridine.

In this solvent and in the presence of triethylamine, the diazaindan-1-one hydrochloride (cf. III) readily condenses with 2-2′-acetanilidovinyl- or 2-alkylthio-derivatives of cyclic quaternary ammonium salts, to yield *mero*cyanine salts or bases, with *p*-dimethylaminobenzaldehyde to give the benzylidene derivative, and with 5-ethoxymethylene-3-ethylrhodanine to give an unsymmetrical oxonol.

Attempts to cyclize the hydrochloride of the acid (II) with hot acetic anhydride gave a dye forming intensely blue solutions in neutral solvents and magenta solutions in acetic or mineral acids. This is believed to be the *meso*methyloxonol (IV; R = Me), possessing properties almost identical with those of the unsubstituted oxonol (IV; R = H) obtained by treating the diazaindan-1-one hydrochloride with ethyl orthoformate in pyridine. These dyes are strongly adsorbed by proteins.



(IV)

The Absorption of Isomeric Dyes.—The Table shows the absorption, in three solvents of differing polarities, of a series of dimethin*mero*cyanines (V) and (VI), and of the oxonol anions and of the p-dimethylaminobenzylidene derivatives of the diazaindanones (I) and (III). Both *p*-dimethylaminobenzylidene derivatives show bathochromic shifts when solvent polarity is increased. This is expected, as related dyes are known to be energetically, highly asymmetric,[5] the energy of the dipolar extreme structure being

* Part VII, *J.*, 1952, 4762.

[1] Knott, *J.*, 1951, 1024.

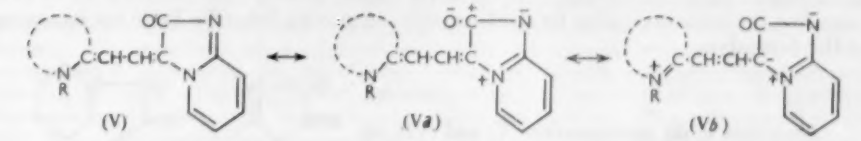
[2] (*a*) Van Dormael, *Bull. Soc. chim. France*, 1949, **58**, 167; (*b*) Knott, *J.*, 1951, 3033.

[3] Bristow, Charlton, Peak, and Short, *J.*, 1954, 616.

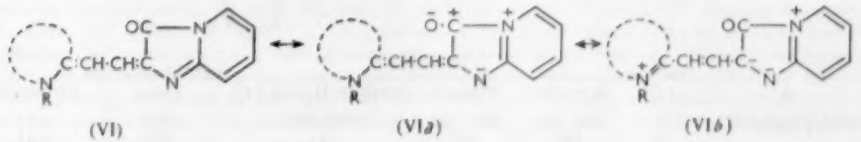
[4] Reindel, *Ber.*, 1924, **57**, 1381.

[5] Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, White, Cressman, and Dent, *J. Amer. Chem. Soc.*, 1951, **73**, 5332.

higher than that of the classical structure. Whereas the shift of the 1-ketone dye when the solvent is changed from pyridine to aqueous pyridine is only 5 mμ, that of the isomer is 31 mμ. This suggests that the former dye is much nearer to the isoenergetic point, as would be expected on the basis of the higher $+M$ effect of the 1-amide (III) compared with the isomer (I) (see below) and of the following considerations. A model of the benzylidene derivative of the 2-amide (I) shows that the two ring systems cannot be coplanar without serious bending of the bridge bond. This overcrowding can best be relieved by the



(V) (V*a*) (V*b*)



(VI) (VI*a*) (VI*b*)

rotation of the bridge bond attached to the phenylene group, which will increase still further its single-bond character and the energetic asymmetry of the molecule, with a resultant hypsochromic effect. On the other hand the deviation [6] from the calculated degenerate mean value is +44 mμ in both cases. This may mean that either the latter value for the 1-amide is too high or that for the isomer is too low. That the latter alternative is almost certain to be true is shown by models and by Fig. 1, a scale drawing of the

FIG. 1.

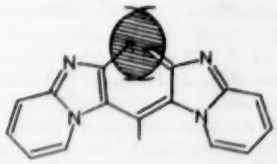
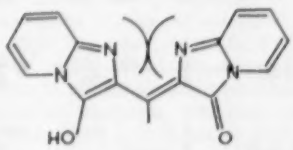


FIG. 2.



2-oxo-oxonol, the value of the absorption of which partly determines the value of the calculated degenerate value of the dye in question. The marked overcrowding of the two oxygen atoms must result in a considerable distortion of the diazaindan-2-one nuclei from coplanarity. The oxonol anion would contain a degenerate resonance system if it were a planar molecule, and it is known that small distortions of the bonds of such a system cause bathochromic shifts. When, however, large distortions occur, sufficient to weaken seriously the π-electron overlap in the system, then a loss of energetic symmetry would result, with a resultant hypsochromic shift. The 1-oxo-oxonol, on the other hand, has, as Fig. 2 shows, a planar molecule.

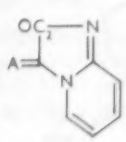
With the exception of the dye (V) derived from 3-ethylbenzoxazoline all the planar *mero*cyanines (V) and (VI) show hypsochromic shifts with increasing solvent polarity (see also Knott [2b]). In general, the shift is larger for the 1-oxo-dye. In the Table, the $-M$ effect of nuclei A and consequently the polarity of the dyes increase on proceeding down the column. The least polar of these dyes, from 3-ethylbenzoxazoline and the 2-amide, still shows a slight bathochromic shift with increasing solvent polarity but this shift is reversed to hypsochromic in its isomer from the 1-amide. This indicates that in the latter case the dipolar extreme structure of the dye is of lower energy than the classical structure and must result from the higher $+M$ effect of diazaindan-1-one (III) compared with that

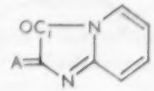
[6] Brooker and Sprague, *J. Amer. Chem. Soc.*, 1941, **63**, 3243.

of the isomer (I). The bathochromic shift of the above dye from the 2-amide is again reversed on replacing 3-ethylbenzoxazoline by 3-ethylbenzothiazoline. This indicates that the latter nucleus has a higher $-M$ effect than the former. Brooker *et al.*,[5] from deviation studies, have shown that this is not always the case, which is more often the reverse.

Proceeding down the Table from 3-ethylbenzoxazoline in the 1-oxo-series and from 3-ethylbenzothiazoline in the 2-oxo-series the energetic asymmetry of the dyes should increase with a resultant increase in the *positive* deviation (to shorter wavelengths) from the calculated mean wavelength. As the Table shows, however, the deviation for all dyes is *negative*, the value decreasing for the 1-oxo-dyes on moving down the Table but increasing for the 2-oxo-dyes.

Absorption of the merocyanines (V) *and* (VI), *etc.*





A	Position of CO	$\lambda_{max.}$ (mμ) Pyridine	Ethanol	Pyridine–H_2O (1 : 4)	Calc. degenerate mean	Deviation
p-NMe_2·C_6H_4·CH:	1	520, 560	520, 562	532, 565	604	+44
	2	480	495	511	555	+44
C:CH·CH:	1	538, 575	522, 558	522, 550	545	−30
	2	497	498	505	496	−8
C:CH·CH:	1	563, 605	555, 593	555, 590	582	−23
	2	(513i), 548	538	537	532	−16
CH·CH:	1	578, 620	600	594	606	−14
	2	557, 595	569	563	556	−39
CH·CH:	1	592, (620i)	562	536	583	−9
	2	570	536	516	534	−36
Oxonol *	1	—	560, 606	—	—	—
(cf. IV; R = H)	2	—	507	—	—	—

* In alcoholic triethylamine. i = inflexion.

If, as discussed above, the calculated degenerate mean for the 2-oxo-*mero*cyanines is lower than the true mean because of the non-planarity of the 2-oxo-oxonol, then the true deviation in the case of the 2-oxo-dyes might well be positive in all cases. This would then lead to decreasing positive deviations on descending the Table, *i.e.* on increasing the dye polarity, which is the reverse of normal. A plausible explanation of these phenomena is lacking.

What is more easily understood is the fact that in isomeric pairs the dyes from the diazaindan-1-one in any particular solvent are deeper in colour than those from the isomer. If one considers the ketonic fragments of these dyes the most important reasonance systems will be (i) (I ⟷ I*a*) and (III ⟷ III*a*) of the amidine-type, in the dipolar form of which, aromaticity of the pyridine ring results, and (ii) the amide-type resonance denoted by the curved arrows in (I*a*) and (III). In the diazaindan-2-one (I) the operation of (ii) is dependent on the operation of (i), whilst in the isomer (III) (ii) and (i) are mutually opposed. This would be expected to endow the compound (III) with a stronger $+M$ effect than its isomer and thus give more polar dyes. The resonance (i) will also have a profound effect on the energies of the excited structures of the dyes. Important contributing structures in these *mero*cyanines in the absence of (i) are contained in (V*a*), (V*b*), and in (VI*a*), (VI*b*). The operation of (i) then increases the significance of forms (V*a* and *b*) by the stabilizing

influence of adjacent atoms of unlike charge, but decreases the significance of forms (VI*a* and *b*) by virtue of the presence of atoms of like charge. According to the author's colour rule [1] the operation of (i) will cause a hypsochromic shift in the dye (V) and a bathochromic shift for the dye (VI); *i.e.*, it will result in a higher intrinsic colour value for the diazaindan-1-one than for the isomer (I), as is the case.

Experimental

N-2-*Pyridylaminoacetic Acid Hydrochloride.*—*N*-2-Pyridylaminoacetonitrile [2] (53 g.) and 5N-hydrochloric acid (250 c.c.) were heated on a steam-bath for 90 min. and then evaporated to dryness. The crystalline cake was ground to a powder and extracted with hot methanol. The extract was evaporated to dryness and the residue was treated with 5N-hydrochloric acid (100 c.c.) as above. The solution was concentrated until a thick meal of crystals separated. These were made into a slurry in propan-2-ol, chilled, and collected. The *hydrochloride* (57 g., 76%) formed almost colourless needles, m. p. *ca.* 190° with previous darkening, from methanol–ether or water (Found: C, 44·2; H, 5·0; N, 14·7; Cl, 18·65. $C_7H_9O_2N_2Cl$ requires C, 44·55; H, 4·75; N, 14·85; Cl, 18·85%). A solution of the hydrochloride (18·85 g.) and sodum hydrogen carbonate (8·4 g.) in boiling water (50 c.c.) solidified on chilling. The free *amino-acid* was washed with a little ice-water and recrystallized from water as colourless needles (12·8 g., 84%), softening at 120° and 165° with m. p. 175° (green), the needles breaking to a powder when washed with methanol (Found: C, 49·1; H, 5·6; N, 16·5. $C_7H_8O_2N_2,H_2O$ requires C, 49·45; H, 5·9; N, 16·45%).

3 : 7a-*Diazaindan*-1-*one Hydrochloride.*—*N*-2-Pyridylaminoacetic acid hydrochloride (10 g.) and phosphorus trichloride (50 c.c.) were heated under reflux on a steam-bath for 3 hr. The solid slowly dissolved, a transitory pink coloration occurred, and crystals slowly separated. Ether (100 c.c.) was added and the pale green grains were collected. They were difficult to purify and had m. p. *ca.* 190° (decomp.) (Found: N, 15·9; Cl, 20·3. $C_7H_7ON_2Cl$ requires N, 16·4; Cl, 20·85%).

Bis-(3 : 7a-*diaza*-2-*indan*-1-*one*)*mesomethylmethinoxonol* (IV; R = Me).—*N*-2-Pyridylaminoacetic acid hydrochloride (5·0 g.) dissolved under reflux in acetic anhydride (10 c.c.) to a yellow solution which rapidly became magenta. The mixture was then allowed to cool to 40°, decomposed by water (50 c.c.), and cooled to 20°, and the dye was precipitated by addition of ammonia. The *product* (1·1 g., 28·4%) formed bronze-green needles, of indefinite m. p., from butanol (Found: C, 65·7; H, 3·85; N, 18·95. $C_{16}H_{12}O_2N_4$ requires C, 65·8; H, 4·1; N, 19·2%).

Bis-(3 : 7a-*diaza*-2-*indan*-1-*one*)*methinoxonol* (IV; R = H).—3 : 7a-Diazaindan-1-one hydrochloride (1·7 g.), pyridine (10 c.c.), and ethyl orthoformate (2 c.c.) were heated over a flame for 2—3 min. The dye separated from the blue solution during this time. The dye, collected from the chilled solution, was dissolved in boiling water containing a little acetic acid, and dilute aqueous ammonia was added slowly. The green flakes (0·55 g., 39·5%) which separated were recrystallized from ethanol, and the *dye* was then obtained as green needles, decomp. from 240° (Found: C, 64·8; H, 3·85; N, 19·75. $C_{15}H_{10}O_2N_4$ requires C, 64·75; H, 3·6; N, 20·15%).

[3 : 7a-*Diaza*-2-*indan*-1-*one*][3-*ethyl*-2-*thio*-5-*thiazolid*-4-*one*]*methinoxonol.*—3 : 7a-Diazaindan-1-one hydrochloride (0·85 g.), 5-ethoxymethylene-3-ethylrhodanine (1·1 g.), pyridine (20 c.c.), and triethylamine (0·8 c.c.) were refluxed for 30 min., then poured into water and chilled overnight. The aqueous layer was decanted from the tar, and the latter was dissolved in ethanol and acidified with acetic acid. The crystals which separated (1·0 g., 65%) were dissolved in aqueous 2N-sodium carbonate and reprecipitated with acetic acid. The *oxonol* was then dissolved in alcoholic triethylamine, and addition of alcoholic acetic acid gave green needles, m. p. indefinite (Found: N, 13·6; S, 21·15. $C_{13}H_{11}O_2N_3S_2$ requires N, 13·75; S, 21·0%).

2-(3-*Ethylbenzoxazolin*-2-*ylidene*-*ethylidene*)-3 : 7a-*diazaindan*-1-*one.*—The hydrochloride (1·7 g.) of the indanone (III), 2-2′-acetanilidovinylbenzoxazole ethiodide (4·35 g.), pyridine (15 c.c.), and triethylamine (1·6 c.c.) were heated on a steam-bath for 15 min. Addition of aqueous sodium carbonate precipitated the *dye base* (51%), forming brown-green threads, m. p. 237—238°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 71·1; H, 5·15; N, 13·6. $C_{18}H_{15}O_2N_3$ requires C, 70·85; H, 4·9; N, 13·75%). Its *hydrochloride*, obtained by passing hydrogen chloride into a solution of the base in benzene, formed magenta needles, m. p. 259—262°, from methanol–ether (Found: Cl, 10·3. $C_{18}H_{15}O_2N_3,HCl$ requires Cl, 10·4%).

2-(3-*Ethylbenzothiazolin*-2-*ylidene*-*ethylidene*)-3 : 7a-*diazaindan*-1-*one.*—Obtained similarly, in 56% yield, this *dye* formed green needles, m. p. 260° (soften at 230°), from methanol (Found: C, 67·1; H, 4·9; N, 12·95. $C_{18}H_{15}ON_3S$ requires C, 67·3; H, 4·65; N, 13·1%). Its *ethiodide*

was obtained in 95% yield in refluxing benzene (2 hr.) as green needles, m. p. 247° (Found: N, 8·55; I, 26·85. $C_{30}H_{28}ON_3IS$ requires N, 8·8; I, 26·6%).

2-(1-*Ethyl*-1 : 2-*dihydroquinolin*-2-*ylidene*-*ethylidene*)-3 : 7a-*diazaindan*-1-*one* was similarly obtained in 70% yield as green needles, m. p. 197°, from methanol (Found: C, 76·1; H, 5·2; N, 13·2. $C_{20}H_{17}ON_3$ requires C, 76·2; H, 5·4; N, 13·35%).

2-(1 : 2-*Dihydro*-1-*methylpyrid*-2-*ylidene*-*ethylidene*)-3 : 7a-*diazaindan*-1-*one Dihydrate*.—2-2′-Anilinovinylpyridine methiodide (3·4 g.), the hydrochloride (1·7 g.) of the amide (III), pyridine (10 c.c.), triethylamine (3 c.c.), and acetic anhydride (1 c.c.) were heated on a steam-bath for 1 hr. The solution gradually became blue. Water (25 c.c.) was added and the orange solution so formed was evaporated almost to dryness. The solid (2·0 g.) was washed with cold water, and dissolved in boiling water, the solution being then filtered and basified with aqueous sodium carbonate. The *dye base* was collected from the chilled solution as green-brown threads, m. p. 124—125° (from water) (Found: C, 62·8; H, 5·8; N, 14·45. $C_{15}H_{13}ON_3,2H_2O$ requires C, 62·75; H, 5·9; N, 14·65%).

2-(3-*Methylbenzothiazolin*-2-*ylidene*)-3 : 7a-*diazaindan*-1-*one*.—2-Ethylthiobenzothiazole ethotoluene-*p*-sulphonate (2·0 g.), the hydrochloride (0·85 g.) of the amide (III), pyridine (10 c.c.), and triethylamine (1·5 c.c.) were heated on a steam-bath for 15 min. Precipitated with aqueous sodium carbonate, the *dye base* (54% yield) formed orange needles, m. p. 256°, from benzene–ethanol (Found: C, 65·2; H, 4·2; N, 14·2. $C_{16}H_{13}ON_3S$ requires C, 65·0; H, 4·4; N, 14·25%).

2-(1 : 2-*Dihydro*-1-*methylquinolin*-2-*ylidene*)-3 : 7a-*diazaindan*-1-*one*, obtained similarly in 58% yield, formed olive-green needles, m. p. 190°, from methanol (Found: C, 74·4; H, 4·9; N, 15·15. $C_{17}H_{13}ON_3$ requires C, 74·15; H, 4·75; N, 15·3%).

2-p-*Dimethylaminobenzylidene*-3 : 7a-*diazaindan*-1-*one*.—*p*-Dimethylaminobenzaldehyde (1·5 g.), the hydrochloride (1·7 g.) of the amide (III), pyridine (10 c.c.), and triethylamine (1·5 c.c.) were heated on a steam-bath for 30 min. Addition of aqueous sodium carbonate gave 1·2 g. (45%) of *dye*, forming purple needles, m. p. 199°, from ethanol (Found: C, 72·4; H, 5·8; N, 15·65. $C_{14}H_{15}ON_3$ requires C, 72·4; H, 5·65; N, 15·85%).

The author thanks Mrs. M. E. Weston for the preparation of some of the intermediates, Mr. C. B. Dennis for microanalyses, and Mr. R. Searle for absorption measurements.

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276. *Aryl-2-halogenoalkylamines. Part XVI.* The Preparation of Derivatives of 4-[Di-(2-chloroalkyl)amino]azobenzenes.*

By W. C. J. Ross and G. P. Warwick.

The preparation is described of certain mono-, di-, and tri-substituted derivatives of 4-[di-(2-chloroalkyl)amino]azobenzenes. A brief report on the activity of the compounds as tumour-growth inhibitors is given.

In Part XIV [1] was outlined a new approach to the preparation of potentially cytotoxic compounds. This concerned aryldi-(2-chloroethyl)amines in which the chlorine atoms were relatively unreactive but which would become activated in a chemical sense if the molecule underwent a change such as could readily occur *in vivo*. Derivatives of the azo-compound (I) appeared to be particularly suitable for investigation since most of the parent substances contain chlorine atoms of low chemical reactivity whereas reduction products (hydrazo-compounds or amines), possibly formed in the organism,[2] would certainly be more reactive. This compound and its 2′-carboxy-derivative are known to inhibit the growth of the transplanted Walker rat carcinoma, whereas the 4′-nitro- and 3′- and 4′-carboxy-derivatives are inactive.[3] Accordingly a large number of substituted 4-[di-(2-chloroalkyl)amino]azobenzenes has now been synthesised and examined.

* Part XV, *J.*, 1955, 3835.

[1] Ross, Warwick, and Roberts, *J.*, 1955, 3110.
[2] Hamon, *Ann. Chim.* (*France*), 1947, **2**, 233.
[3] Haddow, *Ann. Report Brit. Empire Cancer Campaign*, 1952, **30**, 28; 1953, **31**, 9; Everett, Roberts, and Ross, *J.*, 1953, 2386.

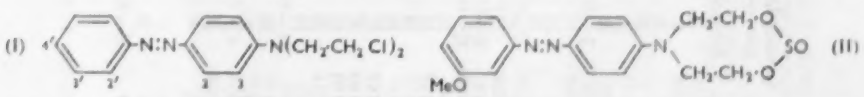
Most of the compounds were prepared by coupling the diazonium salt obtained from the appropriate amine with *NN*-di-(2-chloroethyl)aniline or with its *o*- or *m*-substituted derivative. It was not possible to prepare a stable diazonium salt from *NN*-di-(2-chloroethyl)-*p*-phenylenediamine and so the alternative route employing this intermediate could not be followed.

Our results support the generally accepted view that the diazonium cation is an electrophilic reagent and that electron-releasing substituents *ortho* to the point of coupling facilitate reaction. For example, all the 2-methyl and 2-methoxy-derivatives of compound (I) were very readily obtained—even the diazonium salt derived from *o*-anisidine which did not couple with *NN*-di-(2-chloroethyl)aniline gave these 2-substituted compounds. On the other hand, an *ortho*-carboxy-group hindered the reaction and only the powerfully coupling salts derived from *p*-nitroaniline and *o*-cyanoaniline yielded 2-carboxy-derivatives of (I). The 2 : 2′-dicarboxy-derivative could not be obtained by direct coupling or by acid hydrolysis of the 2-carboxy-2′-cyano-derivative; in this case as elsewhere vigorous acid treatment resulted in the decomposition of the azo-compound.[4]

NN-Di-(2-chloroethyl)-*o*-anisidine did not couple very readily but it afforded 4′-carboxy-4-[di-(2-chloroethyl)amino]-3-methoxyazobenzene in low yield. The low reactivity of *ortho*-substituted arylamines in coupling reactions [5] is considered to be due to the steric restriction placed on the coplanarity of the substituted amino-group with the benzene ring with consequent reduction of electron density at the *para*-coupling position.

It is well established that electron-attracting groups in the aromatic ring of the diazonium compound aid coupling whilst electron-releasing groups hinder it. In accordance, it is now found that whereas the diazonium salt from *m*-toluidine and *m*-anisidine coupled readily with *NN*-di-(2-chloroethyl)aniline the *ortho*- and *para*-isomers required more vigorous conditions: with *o*-anisidine no coupling has occurred under the conditions so far used. Some difficulty was experienced in preparing the 2′-phenyl derivative of (I), but this is probably due to steric hindrance of the coupling reaction. Diazonium salts from the chloro-, bromo-, and nitro-anilines and from *p*-acetylaniline coupled very readily.

Although the diazonium salt from *p*-anisidine did not couple very easily with *NN*-di-(2-chloroethyl)aniline it did so with the more basic *NN*-di-(2-hydroxyethyl)aniline. It was hoped to obtain the required chloroethylamine in better yield by the action of phosphoryl chloride or phosphorus pentachloride on the hydroxyethylaminoazobenzene but experiments with 4-[di-(2-hydroxyethyl)amino]-3′-methoxyazobenzene showed that charring and loss of azo-character occurred. It was considered that this might be due to the acid reaction conditions and so an attempt was made to prepare the chloro-derivative by the action of thionyl chloride in pyridine: the product was apparently the cyclic sulphite (II).



Diazotisation of 2-hydroxy-5-nitroaniline gave a red diazo-oxide which was soluble in methanolic hydrochloric acid. There was little indication of coupling when *NN*-di-(2-chloroethyl)aniline was added to this solution at 0° but 2 hours' heating at 40—50° gave a 25% yield of the required 2′-hydroxy-5′-nitro-derivative. The diazonium compound appeared to be quite stable at this elevated temperature for no appreciable evolution of nitrogen was observed.

Hydrolysis Rates.—The rates of hydrolysis of a selection of the new compounds under the standard conditions [6] have been measured. All but one of the compounds examined have very low chemical reactivity (see Table). The exception is the 4-[di-(2-chloroethyl)-amino]-3-methoxy-derivative whose high reactivity is a consequence of the greater basicity

[4] Cf. Jacobson, *Annalen*, 1909, **367**, 304.
[5] Cf. Friedländer, *Monatsh.*, 1898, **19**, 627; Bamberger, *Ber.*, 1895, **28**, 243; Bamberger and Meimberg, *ibid.*, p. 1891; Gnehm and Blumer, *Annalen*, 1899, **304**, 87.
[6] Ross, *J.*, 1949, 183.

Substituted 4-[di-(2-chloroalkyl)amino]azobenzenes of type (I).

Substituent	Method	M. p.	Solvent	Form	Formula	Found (%): C	H	N	Required (%): C	H	N	Hydrolysis rate[d]	Activity[h]
None[a]	A(i)	73—75°	A	Orange plates	$C_{16}H_{17}N_3Cl_2$	—	—	—	—	—	—	<1%	+ve
2-Me	A(i)	87·5—89	C	Orange prism. needles	$C_{17}H_{19}N_3Cl_2$	60·2	5·7	12·5	60·7	5·7	12·5		(low)
2′-Me	B(ii)[b]	97	A	Red needles	,,	60·6	5·9	12·5	60·7	5·7	12·5		+ve
3′-Me	B(i)	76	A	Orange needles	,,	60·7	5·9	12·6	60·7	5·7	12·5		−ve
4′-Me	B(i)	84	A	Orange needles	,,	60·4	5·8	12·6	60·7	5·7	12·5		−ve
2-MeO	A(i)	79—80	B	Orange plates	$C_{17}H_{19}ON_3Cl_2$	58·2	5·6	11·9	57·9	5·4	11·9		+ve
3′-MeO	B(i)	64—66	J—B	Orange needles	,,	58·0	5·6	12·4	57·9	5·4	11·9		−ve
4′-MeO	B(ii)	104—105	H	Orange needles	,,	57·7	5·5	12·2	57·9	5·4	11·9		−ve
2′-Cl	A(i)	109	H	Red needles	$C_{16}H_{16}N_3Cl_3$	53·5	4·8	12·0	53·9	4·5	11·8		−ve
3′-Cl	A(i)	84	H	Orange plates	$C_{16}H_{16}N_3Cl_3$	53·5	4·7	11·8	53·9	4·5	11·8		−ve
4′-Cl	A(i)	130	H	Golden plates	$C_{16}H_{16}N_3Cl_3$	54·0	4·7	11·7	53·9	4·5	11·8		−ve
2′-Br	A(i)	97—100	H	Orange needles	$C_{16}H_{16}N_3Cl_2Br$	48·0	4·3	10·4	47·9	4·0	10·5		−ve
3′-Br	A(i)	76—78	E—H	Red-orange needles	$C_{16}H_{16}N_3Cl_2Br$	47·9	4·0	10·3	47·9	4·0	10·5		−ve
4′-Br	A(i)	132—134	E—B	Golden needles	$C_{16}H_{16}N_3Cl_2Br$	47·6	4·3	10·7	47·9	4·0	10·5		−ve
2′-I	A(i)	97—98	H	Brown needles	$C_{16}H_{16}N_3Cl_2I$	42·7	3·8	9·4	42·8	3·6	9·4		−ve
2′-CN	A(i)	114—115	H	Red needles	$C_{17}H_{16}N_4Cl_2$	59·3	4·8	15·9	58·8	4·6	16·1		(low)
2′-NO_2	A(i)	119	H	Red needles	$C_{16}H_{16}O_2N_4Cl_2$	52·4	4·5	15·2	52·3	4·4	15·3		−ve
3′-NO_2	A(i)	113	H	Orange needles	$C_{16}H_{16}O_2N_4Cl_2$	52·3	4·6	15·6	52·3	4·4	15·3		−ve
4′-NO_2[a]	A(i)	166—167	F	Red plates	$C_{16}H_{16}O_2N_4Cl_2$	—	—	—	—	—	—	<1%	−ve
2′-CO_2H[d]	A(i)	179—180	F	Orange-red plates	$C_{17}H_{17}O_2N_3Cl_2$	—	—	—	—	—	—	<1%	+ve
3′-CO_2H[d]	A(i)	162—164	G	Yellow needles	,,	—	—	—	—	—	—	<1%	−ve
4′-CO_2H[d]	A(i)	212—214	K	Orange-red plates	,,	—	—	—	—	—	—	<1%	−ve
4′-Ac	A(ii)	136	H	Golden plates	$C_{18}H_{19}ON_3Cl_2$	59·5	5·5	12·1	59·3	5·3	11·5		−ve
2′-Ph	A(i)	92	H—B	Red prisms	$C_{22}H_{21}N_3Cl_2$	65·8	5·5	10·6	66·3	5·3	10·6		−ve
4′-Ph	A(i)	142	B	Golden needles	$C_{22}H_{21}N_3Cl_2$	65·9	5·6	10·6	,,	,,	,,		−ve
2′-SO_3H	C	Indef.	g	Blue needles	$C_{16}H_{17}O_4N_3SCl_2$	47·6	4·5	10·3	47·9	4·3	10·5	<1%	−ve
4′-SO_3H	C	Indef.	g	Blue needles	,,	47·6	4·4	10·3	,,	,,	,,	<1%	−ve
2′-CO_2Me[e]	A(ii)	107—108	H	Red needles	$C_{18}H_{19}O_2N_3Cl_2$	56·6	5·2	11·1	56·9	5·1	11·1		+ve
2′ : 3′-Benzo	B(ii)[f]	103	A	Red prisms	$C_{20}H_{19}N_3Cl_2$	64·8	5·3	11·1	64·5	5·1	11·3		−ve
Analogues containing $N(CH_2{\cdot}CHMeCl)_2$.													
2′-NO_2	A(i)	104	H	Red needles	$C_{18}H_{20}O_2N_4Cl_2$	55·0	5·2	14·3	54·7	5·1	14·2		−ve
4′-NO_2	A(i)	169	E—B	Red needles	$C_{18}H_{20}O_2N_4Cl_2$	54·7	5·3	13·8	54·7	5·1	14·2		−ve

Table continues on opposite page.

Substituted 4-*[di-(2-chloroalkyl)amino]azobenzenes of type* (I). (*Continued.*)

Substituent	Method	M. p.	Solvent	Form	Formula	Found (%): C	H	N	Required (%): C	H	N	Hydrolysis rate[f]	Activity[h]
Analogue containing NEt·CH_2·CH_2Cl.													
2′-CO_2H	A(i)	145·5—147·5°	G	Red needles	$C_{17}H_{19}O_2N_3Cl$	61·1	5·3	12·8	61·5	5·5	12·6		−ve
2-MeO : 2′-Me	A(i)	99—101	B	Red needles	$C_{18}H_{21}ON_3Cl_2$	59·3	6·1	11·2	59·0	5·8	11·5		+ve
2-Me : 4′-MeO	A(ii)	98	H	Orange plates	,,	58·8	5·8	11·6	59·0	5·8	11·5	<1%	+ve
2-MeO : 2′-MeO	A(i)	138—139	E—A	Red-orange needles	$C_{18}H_{21}O_2N_3Cl_2$	56·4	5·7	11·2	56·6	5·5	11·0		(low)
2-MeO : 2′-OH	A(ii)	136—138	H	Brown needles	$C_{17}H_{19}O_2N_3Cl_2$	55·4	5·3	11·5	55·4	5·2	11·4		−ve
2-Me : 2′-Cl	A(i)	122—123	H	Orange needles	$C_{17}H_{18}N_3Cl_3$	54·8	5·0	11·6	55·1	4·9	11·3		−ve
2′-Me : 3′-Cl	A(i)	98—99	H	Red-brown needles	$C_{17}H_{18}N_3Cl_3$	55·2	5·2	11·4	55·1	4·9	11·3		−ve
2′-Me : 4′-Cl	A(i)	78—80	H	Tan needles	,,	54·6	5·1	11·5	55·1	4·9	11·3		−ve
2′ : 3′-Cl_2	A(i) [c]	135	H	Red needles	$C_{16}H_{15}N_3Cl_4$	48·9	4·1	10·8	49·1	3·9	10·8	<1%	−ve
2′ : 4′-Cl_2	A(i) [c]	109—110	H	Orange-red needles	,,	49·1	4·2	10·8	49·1	3·9	10·8		−ve
3′ : 4′-Cl_2	A(i) [c]	88	H	Golden plates	,,	49·3	4·1	10·6	49·1	3·9	10·8		−ve
2-Me : 2′-NO_2	A(i)	148	H	Red needles	$C_{17}H_{18}O_2N_4Cl_2$	53·5	4·8	14·6	53·6	4·8	14·7		−ve
3-MeO : 3′-NO_2	A(i)	120—121	H	Red needles	$C_{17}H_{18}O_2N_4Cl_2$	51·6	4·8	14·1	51·3	4·6	14·1		
3-MeO : 4′-NO_2	A(i)	131—132	H	Red needles	$C_{17}H_{18}O_2N_4Cl_2$	51·3	4·9	14·3	51·3	4·6	14·1		
2′ : 4′-$(NO_2)_2$	A(i) [d]	186—189	H	Red needles	$C_{16}H_{15}O_4N_5Cl_2$	47·0	3·8	17·1	46·6	3·7	17·0		−ve
2′-OH : 5′-NO_2	D	166	E	Red needles	$C_{16}H_{16}O_3N_4Cl_2$	50·2	4·3	14·3	50·1	4·2	14·6		(low)
2-Me : 2′-CO_2H	A(i)	190—191	F	Red needles	$C_{18}H_{19}O_2N_3Cl_2$	56·6	5·1	10·8	56·8	5·0	11·1	<1%	+ve
2-Me : 4′-CO_2H	A(i)	223	H	Orange needles	$C_{18}H_{19}O_2N_3Cl_2$	56·6	5·1	11·4	56·8	5·0	11·1	<1%	+ve
2-MeO : 2′-CO_2H	A(i)	182	H, F	Orange needles	$C_{18}H_{19}O_3N_3Cl_2$	54·8	5·0	10·8	54·6	4·8	10·6	<1%	+ve
3-MeO : 3′-CO_2H	A(i)	132—134	B, D	Orange prisms	$C_{18}H_{19}O_3N_3Cl_2$	54·9	5·0	10·3	54·6	4·8	10·6		
3-MeO : 4′-CO_2H	—	166	G	Orange prism. needles	$C_{18}H_{19}O_3N_3Cl_2$	54·6	4·9	10·7	54·6	4·8	10·6	{Acid 35% {Na salt 21%	+ve
2-CO_2H : 4′-NO_2	A(i)	185—190 [a]	E	Purple plates	$C_{17}H_{16}O_4N_4Cl_2$	50·0	4·1	13·1	49·7	3·9	13·6	<1%	+ve
2-CO_2Me : 4′-NO_2	A(i)	135—138	D	Orange plates	$C_{18}H_{18}O_4N_4Cl_2$	50·4	4·3	13·2	51·4	4·6	13·2		(low)
2-CO_2H : 4′-CO_2H	A(ii)	197	H	Orange powder	$C_{18}H_{17}O_4N_3Cl_2$	52·9	4·0	9·9	52·7	4·2	10·2		+ve
2-CO_2H : 2′-CN	A(i)	213—214	J	Red needles	$C_{18}H_{16}O_2N_4Cl_2$	55·3	4·4	14·4	55·3	4·1	14·3	<1%	+ve
2-Me : 2′ : 3′-benzo	—	118—119	G	Red-purple needles	$C_{21}H_{21}N_3Cl_2$	65·2	5·7	10·8	65·2	5·7	10·9		−ve
2-Me : 4′-Me : 2′-CO_2H	A(i)	204	F	Orange needles	$C_{19}H_{21}O_2N_3Cl_2$	57·7	5·5	10·4	57·9	5·4	10·7	<1%	+ve
2-Me : 2′-OH : 5′-NO_2	D	193—194	E	Red needles	$C_{17}H_{18}O_4N_4Cl_2$	51·5	4·7	14·2	51·4	4·6	14·1		−ve

Solvents used for crystallisation are: A, light petroleum (b. p. 40—60°); B, light petroleum (b. p. 60—80°); C, pentane; D, *cyclo*hexane; E, benzene; F, acetone; G, methanol; H, ethanol; J, ethyl acetate; K, 2-methoxyethanol.

[a] Everett and Ross, *J.*, 1949, 1972. [b] Reaction time 2 weeks. [c] Reaction time 5 weeks. [d] Ref. 3. [e] Also prepared by the action of diazomethane on the acid. [f] Reaction time 1 week. [g] See Experimental section. [h] As inhibitors of the growth of the transplanted Walker rat carcinoma. [i] Diazotisation of amine as outlined by Saunders (ref. 7) see also Noelting and Kopp, *Ber.*, 1905, **38**, 3506. [j] Diazotisation of amine as outlined by Saunders (ref. 7). [k] Dependent on the rate of heating. [l] Based on the development of acidity.

of the amino-group due to hindrance of coplanarity with the benzene ring. The stronger basic character is also reflected in the absorption spectrum which will be discussed in a subsequent paper.

Biological Activity.—Monosubstitution in the 3′- and 4′-position of the active parent substance (I) leads in all the examples studied to loss of the biological activity (Table). However, the incorporation of electron-releasing groups into the molecule at the positions *ortho* to the azo-linkage does not lead to deactivation. The 2′-carboxy-derivative comes into this category for its acidic group will be ionised under physiological conditions; the corresponding methyl ester almost certainly owes its activity to hydrolysis *in vivo*. Activity in compounds bearing electron-releasing *ortho*-substituents is confirmed by the results shown in the Table. One of the most effective compounds is the 2′-carboxy-2-methyl-derivative which contains two such substituents. It will be shown in a later paper that *ortho*-substitution often facilitates the reduction of the azo-linkage in neutral solutions. With the exception of the unsubstituted compound (I) and its 4′-carboxy-3-methoxy-derivative all the biologically active compounds have at least one substituent in a position *ortho* to the azo-linkage. Provided that such a substituent is present further substitution in the 3′- and 4′-position does not normally lead to loss of activity. On account of its higher chemical reactivity (see above) 4′-carboxy-4-[di-(2-chloroethyl)amino]-3-methoxy-azobenzene differs from all the other azo-derivatives now described in that reductive fission of the azo-linkage is probably not necessary to produce an active compound.

Experimental

Preparation of Azo-compounds.—Method A (i). The amine (0·02 mole), in concentrated hydrochloric acid (6 ml.) and water (10 ml.), was converted into the diazonium salt by addition of sodium nitrite (0·02 mole) in water (5 ml.), then added with stirring to a solution of the appropriate aryldi(chloroalkyl)amine (0·02 mole) in ethanol (150 ml.) at 10°. After 12 hr. at 0° the product was collected.

Method A (ii). As A (i), but the reaction time was one week.

Method B (i). The amine (0·08 mole) in concentrated hydrochloric acid (24 ml.) and water (25 ml.) was converted into the diazonium salt by the addition of sodium nitrite (0·08 mole) in water (15 ml.), and ethanol (100 ml.) was added. The aryldi(chloroalkyl)amine (0·02 mole) in ethanol (100 ml.) was added dropwise during 1 hr. to the ice-cooled solution. Stirring was continued for 3 hr. and then the mixture was left overnight at 0°.

Method B (ii). As B (i) but the reaction time was 1—5 weeks.

Method C (for the preparation of the azo-sulphonic acids). The precipitated diazonium salt obtained from the amino-sulphonic acid (0·02 mol.) as described by Saunders [7] was suspended in ethanol (100 ml.) and to this was added the aryldi(chloroalkyl)amine (0·02 mol.) in ethanol (150 ml.). Stirring was continued at room temperature for 3 days and then the azo-compound was collected. The azo-sulphonic acids were crystallised from the minimum amount of hot water rendered alkaline by sodium hydroxide (2N). Addition of an excess of hydrochloric acid (10N) to the hot filtered solution, followed by slow cooling, gave deep blue needles of indefinite m. p.

Method D. The nitro-amine was diazotised as in method A (i). The precipitated diazo-oxide was dissolved in concentrated hydrochloric acid (20 ml.), and methanol (50 ml.) was added. The filtered solution was poured into a solution of the aryldi(chloroalkyl)amine (0·02 mole) in methanol (125 ml.), heated at 40—50° for several hours, then kept at 0° overnight; the azo-compound separated.

The *products* are recorded in the Table.

Attempted Conversion of 4-Amino-NN-di-(2-hydroxyethyl)-3′-methoxyazobenzene into the Di-2″-chloroethyl Derivative.—Thionyl chloride (2 ml.) was added to a cooled solution of the hydroxyethylaminoazo-compound (2 g.) in pyridine (20 ml.). After ¾ hr. at room temperature the mixture was heated for 5 min. at 90°, then evaporated to dryness under reduced pressure. A benzene solution of the residue was passed through a column of activated alumina. The eluates contained an orange solid which after several crystallisations from ethanol gave orange needles, m. p. 149·5° (Found: C, 56·0; H, 5·3; N, 11·5; S, 9·3. $C_{17}H_{19}O_4N_3S$ requires C, 56·5; H, 5·3; N, 11·6; S, 8·9%), which appeared to be the *cyclic sulphite* (II).

[7] Saunders, "The Aromatic Diazo-compounds," Arnold, London, 1949, p. 10.

Hydrolysis Rates of the Di(chloroethyl)aminoazo-derivatives.—These were determined as described by Ross,[6] the least volume of 50% aqueous acetone being used to effect solution. The acidity developed during the hydrolysis was determined by potentiometric titration.

This investigation was supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, and was carried out during the tenure of one of us (G. P. W.) of an overseas C.S.I.R.O. research studentship. The authors thank Professor A. Haddow for permission to quote the results of tumour inhibition studies.

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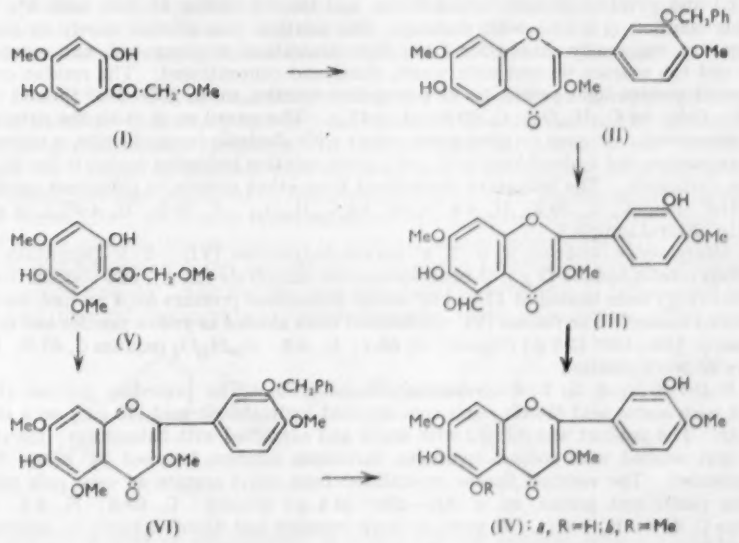
277. *Synthesis of Oxyayanin-B.*

By R. N. GOEL, A. C. JAIN, and T. R. SESHADRI.

The partial methyl ether, oxyayanin-B (IV*a*), has been synthesised by two methods.

A GENERAL method for the synthesis of flavonols of the quercetagetin series was recently described [1] which is particularly suitable for the preparation of partial methyl ethers having 5- and 6-hydroxyl groups. Oxyayanin-B [2] has now been synthesised; 3′-benzyloxy-6-hydroxy-3 : 7 : 4′-trimethoxyflavone (II), prepared by the Allan–Robinson reaction from 2 : 5-dihydroxy-ω : 4-dimethoxyacetophenone (I) and the anhydride and sodium salt of *O*-benzyl*iso*vanillic acid, was condensed with hexamine. During hydrolysis of the



product with hydrochloric acid, debenzylation also occurred, yielding 5-formyl-6 : 3′-dihydroxy-3 : 7 : 4′-trimethoxyflavone (III). Subsequent Dakin oxidation yielded oxyayanin-B (IV*a*) having all the properties of the natural sample.

[1] Jain, Seshadri, and Sreenivasan, *J.*, 1955, 3908.
[2] King, King, and Stokes, *J.*, 1954, 4587.

The older method of Row and Seshadri [3] can also be used. Allan–Robinson condensation of 2 : 5-dihydroxy-ω : 4 : 6-trimethoxyacetophenone (V) with the anhydride and sodium salt of *O*-benzyl*iso*vanillic acid yielded 3′-benzyloxy-6-hydroxy-3 : 5 : 7 : 4′-tetramethoxyflavone (VI) which underwent smooth debenzylation (to IV*b*) and partial demethylation in the 5-position, to form oxyayanin-B (IV*a*).

Experimental

3′-Benzyloxy-6-hydroxy-3 : 7 : 4′-trimethoxyflavone (II).—2 : 5-Dihydroxy-ω : 4-dimethoxyacetophenone (4 g.), *O*-benzyl*iso*vanillic anhydride (32 g.), and sodium *O*-benzyl*iso*vanillate (8 g.) were heated under reduced pressure at 180—184° for 4 hr. and the cooled product refluxed with 8% alcoholic potassium hydroxide (80 c.c.) for 30 min. After removal of alcohol in a vacuum and dissolution of the residue in water (200 c.c.), carbon dioxide was passed through the solution. The yellow precipitate (3·5 g.) crystallised from alcohol as deep yellow rectangular prisms, m. p. 190—191° (Found : C, 69·3; H, 5·2. $C_{25}H_{22}O_7$ requires C, 69·1; H, 5·1%). This *flavone* gave no colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide.

5-Formyl-6 : 3′-dihydroxy-3 : 7 : 4′-trimethoxyflavone (III).—The preceding flavone (3·0 g.) was heated with acetic acid (150 c.c.) and hexamine (12 g.) on a boiling-water bath for 7 hr. Boiling dilute hydrochloric acid (1 : 1; 70 c.c.) was then added and heating continued for 30 min. more. The resulting mixture was cooled, diluted with water, and extracted exhaustively with chloroform. The chloroform layer was washed with sodium hydrogen carbonate solution followed by water, dried, and treated with ether. The insoluble impurities were filtered off and the clear orange solution was concentrated. The residual *aldehyde* crystallised from benzene as very pale yellow prisms, m. p. 209—211° (0·8 g.). It gave a reddish-brown colour with alcoholic ferric chloride and was soluble in 5% aqueous sodium carbonate (Found : C, 61·2; H, 4·8. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%). The 2 : 4-dinitrophenylhydrazone crystallised from acetic acid as orange-yellow needles, m. p. 286° (decomp.).

Oxyayanin-B (IV*a*).—The aldehyde (0·5 g.) was dissolved in 6% aqueous sodium hydroxide (3·5 c.c.) and pyridine (5 c.c.), cooled in ice, and treated during 15 min. with 5% hydrogen peroxide solution (1·5 c.c.) with shaking. The mixture was allowed slowly to reach room temperature, vigorously shaken for 2 hr., then neutralised to Congo-red, and extracted with ether, and the extract washed with water, dried and concentrated. The residue crystallised from ethyl acetate–light petroleum as pale yellow needles, m. p. 207—208° (Found : C, 60·1; H, 4·5. Calc. for $C_{18}H_{16}O_8$: C, 60·0; H, 4·4%). The mixed m. p. with the natural sample was undepressed. It gave an olive-green colour with alcoholic ferric chloride, a crimson colour with magnesium and hydrochloric acid, and a green solution becoming orange in hot 5% aqueous sodium carbonate. The triacetate crystallised from ethyl acetate as colourless needles, m. p. 214—216° (Found : C, 59·2; H, 4·8. Calc. for $C_{24}H_{22}O_{11}$: C, 59·2; H, 4·5%), in agreement with the natural sample.[3]

3′-Benzyloxy-6-hydroxy-3 : 5 : 7 : 4′-tetramethoxyflavone (VI).—2 : 5-Dihydroxy-ω : 4 : 6-trimethoxyacetophenone (3 g.), *O*-benzyl*iso*vanillic anhydride (25 g.), and sodium *O*-benzyl*iso*vanillate (6 g.) were heated at 175—180° under diminished pressure for 4 hr. and worked up as mentioned earlier. The *flavone* (VI) crystallised from alcohol as yellow needles and rectangular rods, m. p. 168—169° (3·5 g.) (Found : C, 66·7; H, 5·2. $C_{26}H_{24}O_8$ requires C, 67·2; H, 5·2%). It gave no ferric reaction.

6 : 3′-Dihydroxy-3 : 5 : 7 : 4′-tetramethoxyflavone (IV*b*).—The preceding flavone (1 g.) was heated with acetic acid (30 c.c.) and concentrated hydrochloric acid (15 c.c.) on a steam-bath for 1 hr. The product was diluted with water and extracted with chloroform; the chloroform layer was washed with sodium hydrogen carbonate solution followed by water, dried, and concentrated. The residual *flavone* crystallised from ethyl acetate as very pale yellow rectangular plates and prisms, m. p. 236—238° (0·4 g.) (Found : C, 60·6; H, 4·7. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). It gives no ferric reaction and dissolves easily in aqueous sodium hydroxide to a yellow solution.

Oxyayanin-B (IV*a*).—(*a*) The above 6 : 3′-dihydroxyflavone (0·25 g.) was refluxed with anhydrous aluminium chloride (1 g.) in dry ether (20 c.c.) for 6 hr., ether was distilled off, and the complex decomposed with dilute hydrochloric acid. The pale yellow precipitate (0·15 g.) was collected, dried, and acetylated by acetic anhydride–pyridine. The acetate crystallised

[3] Row and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23***A*, 24.

from ethyl acetate as colourless needles, m. p. 214—216°. It was deacetylated by refluxing alcoholic hydrochloric acid (1 : 1; 15 c.c.) for 1 hr. Alcohol was distilled off and water added to the remaining mixture; oxyayanin-B, which separated, crystallised from ethyl acetate as pale yellow needles, m. p. and mixed m. p. 207—208°.

(*b*) 3′-Benzyloxy-6-hydroxy-3 : 5 : 7 : 4′-tetramethoxyflavone (VI) (0·5 g.) was refluxed with concentrated hydrochloric acid (30 c.c.) and acetic acid (20 c.c.) for 6 hr. The product was treated with crushed ice and extracted with chloroform. The extract, treated as above, yielded oxyayanin-B triacetate, m. p. 214—216°, and thence oxyayanin-B (0·2 g.).

We are grateful to Professor F. E. King for a sample of natural oxyayanin-B.

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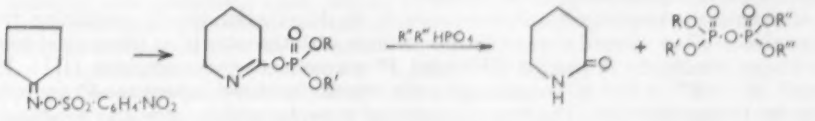
278. *Nucleotides. Part XXXV.** cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate as an Intermediate in the Synthesis of Nucleotide Derivatives: an Alternative Synthesis of Adenosine-5′ Triphosphate.*

By B. H. CHASE, G. W. KENNER, SIR ALEXANDER R. TODD, and R. F. WEBB.

The recently discovered imidoyl phosphate route to esters of pyrophosphoric acid [1,2] has been successfully applied to the synthesis of tribenzyl 2′ : 3′-O-*iso*propylideneuridine-5′ pyrophosphate and hence of uridine-5′ pyrophosphate. Simultaneous production of the related symmetrical pyrophosphates could only be avoided when the initial condensation was carried out in non-polar solvents. The problems associated with the application of the method in the nucleotide field are discussed and the use of unprotected nucleotides is exemplified by syntheses of P^1-benzyl P^2-adenosine-5′ pyrophosphate and adenosine-5′ triphosphate in which the value of long-chain alkylamines for bringing nucleotides into solution has also been demonstrated.

THE major nucleotide coenzymes are unsymmetrical P^1P^2-diesters of pyrophosphoric acid and we have therefore in recent years devoted considerable attention to the development of methods for pyrophosphate synthesis. In Part XIII [2] of our related series "Studies on Phosphorylation" available methods were reviewed and a new method of potential value in the coenzyme field was presented. This method depended on the Beckmann rearrangement of an oxime ester, preferably *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (I) in presence of a salt of a dialkyl phosphate, to give an imidoyl phosphate (II). The intermediate (II) was not isolated but was directly subjected to phosphorolysis producing a tetra-alkyl pyrophosphate. The method was tested in the synthesis of tetrabenzyl pyrophosphate and dibenzyl diphenyl pyrophosphate under various conditions. The present



(I) (II) (III)

paper presents the results of experiments in which the method has been applied in the nucleotide field.

The synthesis of uridine-5′ pyrophosphate, which has been thoroughly explored by using

* Part XXXIV, *J.*, 1955, 4396.

[1] Atherton, Morrison, Cremlyn, Kenner, Todd, and Webb, *Chem. and Ind.*, 1955, 1183.
[2] Kenner, Todd, and Webb, *J.*, 1956, 1231.

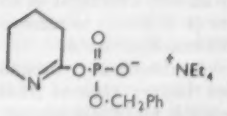
the phosphorochloridate route,[3,4] provided a convenient starting point. Benzyl 2′ : 3′-O-*iso*propylideneuridine-5′ phosphate [5] was converted into its tetra-*n*-butylammonium salt and then brought into reaction with *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (I). The intermediate (II; R = 2′ : 3′-O-*iso*propylideneuridine-5′; R′ = benzyl) was treated directly with dibenzyl hydrogen phosphate in benzene solution, and the protecting groups were removed from the product (III; R = 2′ : 3′-O-*iso*propylideneuridine-5′, R′ = R″ = R‴ = benzyl) by treatment with *m*-cresol [4,6] followed by hydrogenolysis in acidic solution. The final product was examined by paper electrophoresis both in disodium hydrogen phosphate and in potassium dihydrogen phosphate solution, since neither paper nor ion-exchange chromatography resolved satisfactorily mixtures of uridine-5′ pyrophosphate and P^1P^2-di(uridine-5′) pyrophosphate. It was thus established that the product contained uridine-5′ pyrophosphate (yield, 40%) and uridine-5′ phosphate as the sole nucleotidic constituents; no trace of the diuridine pyrophosphate could be detected. When, however, the same sequence of operations was performed with triethylammonium or tetraethylammonium salts of the nucleotide derivative in nitromethane the product contained both uridine-5′ pyrophosphate and P^1P^2-di(uridine-5′) pyrophosphate, the latter being the major nucleotidic component. These results confirm our earlier conclusion [2] that the oxime sulphonate route is satisfactory for the synthesis of unsymmetrical pyrophosphates provided that non-polar solvents are employed: in polar solvents exchange reactions between the imidoyl phosphate and phosphate anions (as well as similar reactions involving the unsymmetrical pyrophosphate) are favoured and the unsymmetrical pyrophosphate is obtained in a complex mixture with the two related symmetrical esters.

It was pointed out earlier that the removal of protecting groups without disrupting the molecule may be, at times, a formidable difficulty in the last stages of coenzyme synthesis, and it was therefore desirable to explore the application of the oxime sulphonate route to less fully protected nucleotides. True, the starting materials in such applications would almost certainly be insoluble in non-polar media and, indeed, special methods would have to be employed to get them into solution, even in solvents such as dimethylformamide or nitromethane. On the other hand, if free nucleotides rather than their monoesters were employed, the disadvantages of polar media might be offset to some extent by the reduced tendency to exchange reactions shown by diesters as compared with tetraesters of pyrophosphoric acid. It was found after a number of trials that tri-*n*-octylamine can be used to bring many nucleotides into solution in dimethylformamide. Benzyl adenosine-5′ phosphate,[7] an extremely insoluble nucleotide derivative, is only slightly soluble in a mixture of tri-*n*-octylamine and dimethylformamide but a suspension in this medium was treated with our reagent (I). P^1P^2-Dibenzyl P^1P^2-di(adenosine-5′) pyrophosphate was produced since P^1P^2-di(adenosine-5′) pyrophosphate [8] was obtained after debenzylation with sodium iodide.[9] The yield from this reaction was low (18%), doubtless because of the low solubility of the benzyl adenosine-5′ phosphate and the consequent rearrangement of the oxime ester (I) to the imidoyl sulphonate; it has already been shown that if the Beckmann rearrangement of the oxime ester is allowed to occur before any phosphate is added the yield of pyrophosphate is reduced.[2]

Adenosine-5′ phosphate dissolves completely in dimethylformamide containing tri-*n*-octylamine. When allowed to react in this medium with the ester (I) in presence of benzyl dihydrogen phosphate it yielded P^1-benzyl P^2-adenosine-5′ pyrophosphate (III; R = benzyl, R′ = R″ = H, R‴ = adenosine-5′) which furnished adenosine-5′ pyrophosphate on hydrogenolysis. The two symmetrical pyrophosphates were also produced in the reaction, but in a series of experiments the yield of benzyl adenosine-5′ pyrophosphate (30—40%) was rather higher than that of di(adenosine-5′) pyrophosphate (30%); a substantial amount of adenosine-5′ phosphate (30%) was recovered unchanged. It seemed

[3] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.
[4] Kenner, Todd, Webb, and Weymouth, *J.*, 1954, 2288.
[5] Corby, Kenner, and Todd, *J.*, 1952, 3669.
[6] Curry, Ph.D. Thesis, Cambridge, 1952; Kenner and Mather, to be published.
[7] Baddiley and Todd, *J.*, 1947, 648.
[8] Christie, Elmore, Kenner, Todd, and Weymouth, *J.*, 1953, 2947.
[9] Cremlyn, Kenner, Mather, and Todd, to be published.

possible that formation of the symmetrical products might be greatly reduced by conducting the reaction in two stages and using tetra-alkylammonium rather than trialkylammonium salts; for, although polar solvents would be employed, an imidoyl phosphate such as (IV) would be unlikely to undergo exchange of phosphate anions in presence of another phosphate. However we were unable to detect any reaction between the salt (IV) [prepared from the ester (I) and bistetraethylammonium benzyl phosphate] and uridine-5′ phosphate. From these results we conclude that the scope of the imidoyl phosphate method in effecting the condensation of trialkylammonium salts in dimethylformamide solution is generally similar to the earlier carbodi-imide method for pyridinium salts in pyridine solution.[10]



(IV)

In any given instance one or other method may be preferred, but neither provides a direct logical synthesis of unsymmetrical P^1P^2-diesters of pyrophosphoric acid unaccompanied by symmetrical esters. The provision of such a synthetic route of general application would render the preparation of nucleotide coenzymes in quantity comparatively easy, and further experiments to this end will be reported later.

The carbodi-imide method has been applied with considerable success to the preparation of adenosine-5′ triphosphate[11] and uridine-5′ triphosphate.[12] It seemed worthwhile trying the oxime sulphonate method in the same kind of procedure, *i.e.*, condensation of adenosine-5′ phosphate with excess of orthophosphoric acid. Anion-exchange chromatography[13] showed that a 40% yield of adenosine-5′ triphosphate was produced by the reaction between adenosine-5′ phosphate (1 mol.), orthophosphoric acid (10 mols.), tri-*n*-octylamine (24 mols.), and *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (I) (7 mols.). The main difficulty in preparations of this general type lies in the separation of the desired product from the large quantities of inorganic polyphosphates produced; selective precipitation of the mercuric salts according to the classical method of Lohmann[14] leads to considerable losses. A convenient solution to the problem has been found in extraction with ethyl acetate containing tri-*n*-decylamine, the nucleotidic materials being then preferentially retained in the aqueous layer. After a few stages of countercurrent extraction, the nucleotides can be separated by anion-exchange chromatography in the usual way and the adenosine-5′ triphosphate isolated as its barium salt.

Experimental

Tetra-n-*butylammonium Benzyl 2′ : 3′-O-iso*Propylideneuridine-5′ *Phosphate.*—Benzyl 2′ : 3′-O-*iso*propylideneuridine-5′ phosphate[5] (0·614 g.) was added in small portions to a vigorously stirred suspension of silver carbonate (0·6 g.) in water (5 c.c.). The mixture was stirred for 15 min., then filtered, and the excess of silver carbonate was washed with water (5 c.c.) and acetone (5 c.c.). The combined filtrate and washings were refluxed for 20 min. with tetra-*n*-butylammonium iodide[15] (0·369 g., 1 mol.), the mixture was filtered, and the precipitated silver iodide washed with acetone (10 c.c.) and water (10 c.c.). The combined filtrate and washings were evaporated under reduced pressure and finally dried *in vacuo* over phosphoric oxide, yielding *tetra*-n-*butylammonium benzyl 2′ : 3′-O-isopropylideneuridine-5′ phosphate* (0·81 g., 94%) as a colourless gum slightly soluble in benzene and readily so in chloroform and ethyl methyl ketone (Found: N, 6·0; P, 4·3. $C_{35}H_{58}O_9N_3P$ requires N, 6·0; P, 4·5%).

Uridine-5′ Pyrophosphate by Use of Tetra-n-*butylammonium Benzyl 2′ : 3′-O-iso*Propylideneuridine-5′ *Phosphate.*—The above tetra-*n*-butylammonium salt (0·213 g.) in ethyl methyl ketone (1 c.c.) and benzene (1 c.c.) was treated with *cyclo*pentanone oxime *p*-nitrobenzenesulphonate[5] (0·072 g., 1 mol.), and the solution refluxed for 2 hr. and then evaporated under reduced pressure. A solution of dibenzyl hydrogen phosphate (0·069 g., 1 mol.) in benzene (2 c.c.) was then added, and the mixture refluxed for 1½ hr. and then set aside at room temperature

[10] Khorana and Todd, *J.*, 1953, 2257; Kenner, Todd, and Webb, *J.*, 1954, 2843.
[11] Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3517.
[12] Hall and Khorana, *ibid.*, p. 5056.
[13] Cohn and Carter, *ibid.*, 1950, **72**, 4273.
[14] Lohmann, *Biochem. Z.*, 1931, **233**, 460.
[15] Hager and Manel, *J. Amer. Chem. Soc.*, 1926, **48**, 2697.

overnight. The solution was washed successively with water (2 c.c.), with 2% sodium hydrogen carbonate solution (2 c.c.), and with water (2 c.c.), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was dissolved in *m*-cresol (2 c.c.), and the solution heated at 40° for 7 min. to effect partial debenzylation. Water (2 c.c.), ethanol (1 c.c.), palladium oxide (*ca.* 5 mg.), and palladised charcoal (*ca.* 5 mg. of 10%) were added and the mixture shaken overnight in an atmosphere of hydrogen. The filtered solution was extracted with ether (4 × 5 c.c.) to remove *m*-cresol, and the aqueous solution neutralised (to pH 7) with aqueous lithium hydroxide.

Examination of the neutralised solution by paper electrophoresis in 0·1M-disodium hydrogen phosphate and in 0·1M-potassium dihydrogen phosphate buffers (see below) showed that uridine-5′ phosphate and uridine-5′ pyrophosphate were the only nucleotidic materials present. Elution of the appropriate areas of the chromatograms with 0·1N-hydrochloric acid and determination of the optical densities of the solutions at 260 mμ showed the ratio of the nucleotides to be : uridine-5′ phosphate 53, uridine-5′ pyrophosphate 47%. The above neutralised solution was evaporated under reduced pressure to 1 c.c., a solution of barium acetate (0·3 g.) in water (1 c.c.) added, and the precipitate collected by centrifugation, washed successively with water (2 c.c.), ethanol (2 × 2 c.c.), and ether (2 c.c.), and dried *in vacuo* over phosphoric oxide. The product (0·16 g.) was shown by paper electrophoresis in the above-mentioned buffers to contain uridine-5′ pyrophosphate as the only nucleotidic material present. Paper chromatography in *iso*propyl alcohol–1% ammonium sulphate solution (3 : 2) confirmed the above finding and showed also the presence of inorganic pyrophosphate after spraying with the perchloric acid–ammonium molybdate reagent.[16] Determination of the ultraviolet absorption of a dilute solution of the product showed that uridine-5′ pyrophosphate accounted for 37% of the weight of the crude material : the yield of barium uridine-5′ pyrophosphate was thus 0·06 g. (40 %). The material behaved exactly as an authentic sample 4 when examined by anion-exchange, paper-chromatographic, and paper-electrophoretic methods.

Other Syntheses of Uridine-5′ Pyrophosphate using cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate.*—(1) To a solution of dibenzyl hydrogen phosphate (0·139 g.) and triethylamine (0·07 c.c., 1 mol.) in nitromethane (2·5 c.c.) *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·142 g., 1 mol.) was added and the solution kept at room temperature for 2 hr. Benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate (0·227 g., 1 mol.) was added, the solution kept at 22° for 17 hr., and the nucleotide fraction isolated and examined by paper electrophoresis as described above; the nucleotide material had the following composition : uridine-5′ phosphate 25, uridine-5′ pyrophosphate 10, P^1P^2-di(uridine-5′) pyrophosphate 65%; all products were identified by comparison with authentic samples.

(2) A solution of dibenzyl hydrogen phosphate (0·278 g.) in water (5 c.c.) and acetone (5 c.c.) was titrated to pH 7 with tetraethylammonium hydroxide solution, then evaporated under reduced pressure, and the residue dried by repeated evaporation with benzene and nitromethane. The dry gum was dissolved in nitromethane (5 c.c.), *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·284 g., 1 mol.) added, and the solution was kept at 25° for 3 hr. Benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate (0·454 g., 1 mol.) was now added and the solution kept at room temperature for 16 hr. The nucleotidic fraction was isolated and examined in the usual manner and shown to have the following nucleotide content : uridine-5′ phosphate 34, uridine-5′ pyrophosphate 12, P^1P^2-di(uridine-5′) pyrophosphate 44%.

(3) When benzyl 2′ : 3′-*O-iso*propylideneuridine-5′ phosphate (1 mol.) was converted into its tetraethylammonium salt and the latter allowed to react in nitromethane first with *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (1 mol.) and then with dibenzyl hydrogen phosphate (1 mol.) the product had the following nucleotide content : uridine-5′ phosphate 42, uridine-5′ pyrophosphate 22, P^1P^2-di(uridine-5′) pyrophosphate 36%.

Reaction of Benzyl Adenosine-5′ Phosphate with cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate.*—Benzyl adenosine-5′ phosphate[7] (0·22 g.) was suspended in a mixture of tri-*n*-octylamine (0·23 c.c.) and dimethylformamide (2·5 c.c.). *cyclo*Pentanone oxime *p*-nitrobenzenesulphonate (0·124 g., 1 mol.) was added and the suspension vigorously shaken for 16 hr., after which the undissolved benzyl adenosine-5′ phosphate (0·1 g.) was filtered off and the filtrate evaporated under reduced pressure. The residue was dissolved in ethyl methyl ketone (10 c.c.), sodium iodide (0·3 g.) added, and the solution heated to reflux : a precipitate was rapidly formed. The solid was collected, washed with acetone (10 c.c.), and dried *in vacuo* over phosphoric oxide. The solid (0·224 g.), when examined by paper chromatography with the solvent systems *iso*propyl alcohol–1% ammonium sulphate (3 : 2) and *n*-butanol–water–acetic acid (5 : 3 : 2), was

[16] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.

found to contain P^1P^2-di(adenosine-5′) pyrophosphate (yield 18%) and unchanged adenosine-5′ benzyl phosphate.

Benzyl Dihydrogen Phosphate (with Dr. A. S. CURRY).—Dibenzyl hydrogen phosphate (8·0 g.) in water (125 c.c.) and ethanol (125 c.c.) was shaken in an atmosphere of hydrogen with palladium oxide (0·4 g.). The rapid uptake of hydrogen was interrupted after 700 c.c. had been absorbed. Catalyst was removed and the solution extracted with chloroform (3 × 250 c.c.). The dried (Na_2SO_4) extract was evaporated under reduced pressure, the residue dissolved in chloroform (50 c.c.), *cyclo*hexylamine (4·35 g.) added, the solution cooled to 5°, and the precipitate (7·2 g.) collected and washed with chloroform. Recrystallisation from aqueous acetone afforded colourless needles (6·4 g., 55%), m. p. 233—235°. When dried *in vacuo* at room temperature ($CaCl_2$) *bis*cyclo*hexylammonium benzyl phosphate* was obtained as the *monohydrate* (Found: C, 56·2; H, 9·1; N, 6·4. $C_{19}H_{35}O_4N_2P,H_2O$ requires C, 56·4; H, 9·2; N, 6·9%). Prolonged "drying" at 90°/1 mm. afforded cyclo*hexylammonium benzyl hydrogen phosphate*, m. p. 233—235° undepressed on admixture with the bis*cyclo*hexylammonium salt (Found: C, 54·4; H, 8·0; N, 4·7. $C_{13}H_{22}O_4NP$ requires C, 54·3; H, 7·7; N, 4·9%). The *benzyl dihydrogen ester* when regenerated from the *cyclo*hexylammonium salt, crystallised from ethanol–benzene in colourless prisms, whose m. p., though sharp, varied between 85° and 118° according to the rate of heating (Found, in material dried *in vacuo* over P_2O_5 at room temperature: C, 45·0; H, 4·7. $C_7H_9O_4P$ requires C, 44·7; H, 4·8%). When the benzyl dihydrogen ester was directly isolated from the hydrogenation of dibenzyl hydrogen phosphate without the intermediate formation of the *cyclo*hexylammonium salt it was invariably accompanied by a second substance which separated from water in colourless prisms, m. p. 188—189° and appeared from its properties to be the "quarter sodium salt"[18] of benzyl dihydrogen phosphate (Found: C, 42·3; H, 4·1. $C_{14}H_{17}O_8P_2Na$ requires C, 42·2; H, 4·3%).

Adenosine-5′ Pyrophosphate from Adenosine-5′ Phosphate, Benzyl Dihydrogen Phosphate and cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate*.—A mixture of adenosine-5′ phosphate[7] (0·035 g.), benzyl dihydrogen phosphate (0·095 g., 5 mols.), tri-*n*-octylamine (0·212 g., 6 mols.), dry benzene (5 c.c.), and dry dimethylformamide (20 c.c.) was concentrated to 4 c.c. at atmospheric pressure, then cooled to room temperature, and *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·12 g., 4 mols.) was added. The mixture was kept at room temperature for 16 hr. and then examined by paper chromatography on Whatman No. 1 paper, using *n*-butanol–acetic acid–water (5 : 2 : 3). Five ultraviolet absorbing areas were present in the developed chromatogram which were identified by comparison with authentic specimens as (*a*) P^1P^2-di(adenosine-5′) pyrophosphate (R_F, 0·10), (*b*) adenosine-5′ phosphate (R_F, 0·30), (*c*) *p*-nitrobenzenesulphonic acid (R_F, 0·64), and (*d*) benzyl dihydrogen phosphate and P^1 : P^2-dibenzyl pyrophosphate, the fifth area (*e*) (R_F, 0·38) being tentatively assumed to represent the hitherto unknown P^1-benzyl P^2-adenosine-5′ pyrophosphate. The reaction mixture was then run as bands on sheets of Whatman No. 1 paper in the above solvent system, and the strips (R_F, 0·38) corresponding to (*e*) above were cut out and eluted with 10% aqueous acetic acid. The extract, after concentration under reduced pressure (to 50 c.c.), was shaken with palladium oxide (20 mg.) in an atmosphere of hydrogen for 18 hr., filtered, and concentrated under reduced pressure. The concentrate was shown by paper electrophoresis in two buffer systems and by paper chromatography (see below) to contain only adenosine-5′ pyrophosphate and a trace of adenosine-5′ phosphate. The yield of P^1-benzyl P^2-adenosine-5′ pyrophosphate (and also of the adenosine-5′ pyrophosphate formed from it) was estimated in the usual way by elution of the appropriate areas of chromatograms with dilute acid and determination of the optical density of the eluates at 260 mμ. In a number of experiments the yield of P^1-adenosine-5′ P^2-benzyl pyrophosphate was 30—40% and that of the accompanying P^1P^2-di(adenosine-5′) pyrophosphate and unchanged adenosine-5′ phosphate were each *ca.* 30%.

Adenosine-5′ Triphosphate.—An anhydrous solution of tri-*n*-octylamine (6 c.c., 24 mols.) and phosphoric acid (from 1·0 g. of "88%" syrupy phosphoric acid; 10 mols.) in dimethylformamide (20 c.c.) was prepared by repeated addition and evaporation of dimethylformamide. Adenosine-5′ phosphate (0·33 g.) was then added and the solution evaporated to 12 c.c. *cyclo*Pentanone oxime *p*-nitrobenzenesulphonate (1·99 g., 7 mols.) was added to the pale yellow syrupy liquid, and the mixture was shaken until homogeneous (30 min.); the solution was kept at room temperature for 15 hr., then diluted with water (20 c.c.), and the mixture evaporated under reduced pressure to 20 c.c. A solution of barium acetate (3·0 g.) in water (28 c.c.) was added, and the precipitate collected by centrifugation, and washed successively with ethanol (20 c.c.), water (20 c.c.), aqueous ethanol (1 : 1; 20 c.c.), ethanol (20 c.c.), and ether (20 c.c.). The crude barium salt so obtained was dried *in vacuo* over phosphoric oxide

at 60° for 2 hr., giving a white powder (1·8 g.). Anion-exchange analysis of this barium salt on Dowex-2 resin (chloride form) showed that the adenosine-5′ triphosphate eluted with 0·1N-hydrochloric acid accounted for 70% of the total nucleotides present.

The above barium salt (1·7 g.) was suspended in ice-water (40 c.c.), and barium precipitated as sulphate by dropwise addition of 0·5N-sulphuric acid. The precipitate was centrifuged off and lithium chloride (1·2 g.) added to the supernatant solution which was then diluted with water to 60 c.c. The solution was used as the lower phase of tube 0 in an eight-stage manually operated counter-current separation where the phases (60 c.c. each) had been previously prepared by equilibrating a solution of tri-*n*-decylamine (8 c.c.) in ethyl acetate (100 c.c.) with a 2% aqueous solution of lithium chloride: the contents of tubes 0—4 were combined, ammonia (4 c.c.; *d* 0·88) added, and the mixture shaken for 30 min. The aqueous layer was separated and put on a column of Dowex-2 resin (chloride form). The column was first eluted with 0·05N-hydrochloric acid (2·8 l.), the eluate being discarded, and then with ice-cold 0·1N-hydrochloric acid, the eluate being collected in a flask cooled to 0°. The first 150 c.c. of the 0·1N-hydrochloric acid eluate were discarded, and the next 1800 c.c. collected and extracted twice with a solution of tri-*n*-decylamine (35 c.c.) in ethyl acetate (500 c.c.). The aqueous solution was then adjusted to pH 8 with lithium hydroxide solution, washed with ethyl acetate (200 c.c.), neutralised (pH 7) with dilute hydrochloric acid, and evaporated, *in vacuo*, to 25 c.c. Addition of barium acetate (2·0 g.) in water (20 c.c.) gave a white precipitate which was collected by centrifugation, washed successively with water, aqueous ethanol, 95% ethanol, and ether, and dried *in vacuo* over phosphoric oxide. The barium adenosine-5′ triphosphate obtained (0·108 g., 33%) was shown by paper chromatography on Whatman No. 1 paper with *iso*propyl alcohol–1% ammonium sulphate (3 : 2) to be the only nucleotidic material present. Determination of orthophosphate [17] showed negligible (0·2%) contamination (Found: N, 7·7; P total, 10·4%; P total/P labile, 1·46. Calc. for $C_{10}H_{12}N_5O_{13}P_3Ba_3.6H_2O$: N, 7·9; P total, 10·5%; P total/P labile, 1·5).

Paper-electrophoretic Data.—All migrations towards the negative pole. Buffer systems: *A*, 0·1M-potassium dihydrogen phosphate; *B*, 0·1M-disodium hydrogen phosphate. Whatman No. 4 paper was used throughout. Uridine derivatives were run for 9 hr. at 200 v; adenosine derivatives for 16 hr. at 150 v. The results are tabulated.

	Migration (cm.) in buffer:		R_P in system:	
	A	*B*	*C*	*D*
Uridine-5′ phosphate	3·7	5·1	0·64	0·29
Uridine-5′ pyrophosphate	5·9	6·0	0·47	0·16
P^1P^2-Di(uridine-5′) pyrophosphate	4·7	3·6	0·45	0·14
Uridine	0	0	—	—
Adenosine-5′ phosphate	5·1	7·8	0·43	0·30
Adenosine-5′ pyrophosphate	8·8	9·3	0·35	—
P^1P^2-Di(adenosine-5′) pyrophosphate	6·6	6·1	0·26	0·09
Adenosine-5′ benzyl phosphate	—	—	0·68	0·61
P^1-Adenosine-5′ P^2-benzylpyrophosphate	—	—	—	0·38
Adenosine-5′ triphosphate	—	—	0·20	—
p-Nitrobenzenesulphonic acid	—	—	0·83	0·66

Paper-chromatographic Data.—Solvent systems: *C*, *iso*propyl alcohol–1% ammonium sulphate (3 : 2) run on Whatman No. 1 paper previously soaked in 1% ammonium sulphate solution and dried; *D*, butan-1-ol–acetic acid–water (5 : 3 : 3) on Whatman No. 1 paper. Results are tabulated.

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[17] Allen, *Biochem. J.*, 1940, **34**, 858.
[18] Brown, Malkin, and Maliphant, *J.*, 1955, 1584.

279. *Triterpenoids. Part XLVIII.* Olean-13(18)-ene: Isomerisation of Olean-12-ene and Related Hydrocarbons with Mineral Acid.*

By George Brownlie, M. B. E. Fayez, F. S. Spring, Robert Stevenson, and W. S. Strachan.

Pure olean-13(18)-ene (I) has been obtained for the first time by methods avoiding the use of mineral acid. Treatment of olean-13(18)-ene (I), olean-12-ene (II), olean-18-ene (germanicene) (III), and 18α-olean-12-ene (IV) with mineral acid gives the same equilibrium mixture of hydrocarbons, crystallisation of which yields a mixed crystal of olean-13(18)-ene (I) and 18α-olean-12-ene (IV). This mixed crystal is identical with the hydrocarbon "β-amyrene-III" obtained by Winterstein and Stein by Clemmensen reduction of olean-12-en-3-one.

Takeda [1] showed that Clemmensen reduction of taraxerone (skimmione; cf. Koller, Hiestand, Dietrich, and Jeger [2]) gives an unsaturated hydrocarbon, $C_{30}H_{50}$, m. p. 189—190°, $[\alpha]_D$ −20·5°, which is identical with "β-amyrene-III," previously obtained by Winterstein and Stein [3] by similar reduction of olean-12-en-3-one. According to Takeda, this hydrocarbon is olean-13(18)-ene (I), a view confirmed by Jones and his collaborators [4, 5] who found, however, that the hydrocarbon prepared by the method of Winterstein and Stein and by the action of hydrochloric–acetic acid on olean-12-ene (II) is appreciably more lævorotatory ($[\alpha]_D$ −33°) than that obtained by Winterstein and Stein; the difference was commented upon by Davy *et al.*[5] who believed that their hydrocarbon was purer. During a study of the triterpenoid ketone friedelin, Brownlie, Spring, Stevenson, and Strachan [6] discovered that treatment of the derived hydrocarbon friedelene with hydrochloric–acetic acid gives an isomer which is indistinguishable from the hydrocarbon obtained by the same treatment of olean-12-ene (II). The specific rotation of this isomer, $[\alpha]_D$ −20°, is in good agreement with the values observed by Takeda [1] for olean-13(18)-ene and by Winterstein and Stein [3] for β-amyrene-III.

The melting points and specific rotations given in the literature for preparations of olean-13(18)-ene (I), in which the reaction mixture had been exposed for a long time to strong mineral acid, are annexed.

Method	M. p.	$[\alpha]_D$ ($CHCl_3$)	Ref.
Clemmensen redn. of olean-12-en-3-one	187—189·5°	−22°	3
Clemmensen redn. of olean-12-en-3-one	191·5—192·5	−32·5	4
Clemmensen redn. of taraxerone	189—190	−20·5	1
Clemmensen redn. of taraxerone	184 (183—184)	−21(−24)	2
Olean-12-ene + HCl–AcOH	190—191	−33	5
Olean-12-ene + HCl–AcOH	186—187	−20	6
"Acid-catalysed" isomerisation of olean-12-ene	186—187	−13·9	*a*
Friedelene + HCl–AcOH	186—187	−20	6
Friedelanol + PhOH + HCl	186—187	−12·5	*a*
Friedelene + $ZnCl_2$–AcOH	183—184	−18	*b*

[a] Corey and Ursprung, *J. Amer. Chem. Soc.*, 1955, **77**, 3668. [b] Dutler, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1955, **38**, 1268.

"β-Amyrene-IV," obtained [3] as an intermediate in the Clemmensen reduction of olean-12-en-3-one to "β-amyrene-III," was shown by Davy *et al.*[5] to be a mixture of

* Part XLVII, *J.*, 1956, 456.

[1] Takeda, *J. Pharm. Soc. Japan*, **1943**, **63**, 197.
[2] Koller, Hiestand, Dietrich, and Jeger, *Helv. Chim. Acta*, 1950, **33**, 1050.
[3] Winterstein and Stein, *Annalen*, 1933, **502**, 223.
[4] Ames, Halsall, and Jones, *J.*, **1951**, 450.
[5] Davy, Halsall, and Jones, *ibid.*, p. 458.
[6] Brownlie, Spring, Stevenson, and Strachan, *Chem. and Ind.*, 1955, 686.

olean-12-ene (II) and olean-13(18)-ene (I). They also showed that the formation of "β-amyrene-IV" is due to the fact that the reaction was not carried to completion. According to Beaton, Spring, Stevenson, and Stewart,[7] a hydrocarbon obtained by a brief Clemmensen reduction of taraxerone by Koller *et al.*[2] is a similar mixture.

The relatively low lævorotations of the hydrocarbons obtained by Corey and Ursprung[8] are not difficult to explain, since the isolation of a hydrocarbon of constant specific rotation from the mixture obtained by acid-isomerisation of olean-12-ene (or from friedelene) requires many crystallisations of the product during which the rotation increases slowly from *ca.* −10° to *ca.* −20°. The high lævorotations observed by Ames *et al.*[4] and by Davy *et al.*[5] are, however, anomalous.

We find that treatment of olean-12-ene with hydrochloric–acetic acid gives a product having $[\alpha]_D$ −10° ± 2°, repeated crystallisation of which yields a hydrocarbon having $[\alpha]_D$ −20° ± 2°. The specific rotation and melting point of this hydrocarbon are not changed by repeated crystallisation or by careful chromatography. The difficulty attending the isolation of the hydrocarbon of $[\alpha]_D$ −20° suggested that the initial reaction product ($[\alpha]_D$ *ca.* −10°) is an equilibrium mixture of isomers. This view was confirmed by the observation that treatment of the hydrocarbon of $[\alpha]_D$ −20°, with hydrochloric–acetic acid regenerates the mixture of $[\alpha]_D$ −10°. If the hydrocarbon, $[\alpha]_D$ −20°, is pure olean-13(18)-ene, this compound is not stable to mineral acid, a decision which led us to prepare olean-13(18)-ene by methods in which mineral acid is not used. Oleana-11 : 13(18)-dien-3β-ol[9] was hydrogenated over platinum prepared from platinum oxide from which traces of water-soluble platinum salts were removed by careful washing. The product, olean-13(18)-en-3β-ol,[10,4] was oxidised by the chromic acid–pyridine complex to olean-13(18)-en-3-one, the physical constants of which are in fair agreement with those of specimens obtained by other methods,[4] with the differences that our preparation does not show a preliminary softening before the melting point and its ultraviolet absorption spectrum does not include low-intensity bands at 2430, 2510, and 2620 Å. Reduction of olean-13(18)-en-3-one by the Wolff–Kishner method gives a hydrocarbon, m. p. 187—188°, $[\alpha]_D$ −48° ± 2°. In contrast with the behaviour of the product obtained by methods in which mineral acid is used, this hydrocarbon is easily purified, and attains a constant specific rotation after one crystallisation. We believe that it is pure olean-13(18)-ene and support for this opinion was obtained as follows.

Oleana-11 : 13(18)-dien-3β-ol was oxidised to oleana-11 : 13(18)-dien-3-one,[11] Wolff–Kishner reduction of which gave oleana-11 : 13(18)-diene, whose constants agree with those given by Ruzicka *et al.*[9] for the hydrocarbon obtained by oxidation of olean-12-ene with selenium dioxide. Hydrogenation of oleana-11 : 13(18)-diene over platinum (from purified platinum oxide) at room temperature gives olean-13(18)-ene, $[\alpha]_D$ −48°, identical with the specimen obtained as described above. Jeger and his collaborators[2] reduced oleana-11 : 13(18)-diene at 70—80° over platinum and obtained a hydrocarbon, $[\alpha]_D$ −27°. The low lævorotation of their product may have been due to the presence of traces of mineral acid in the reaction solution.

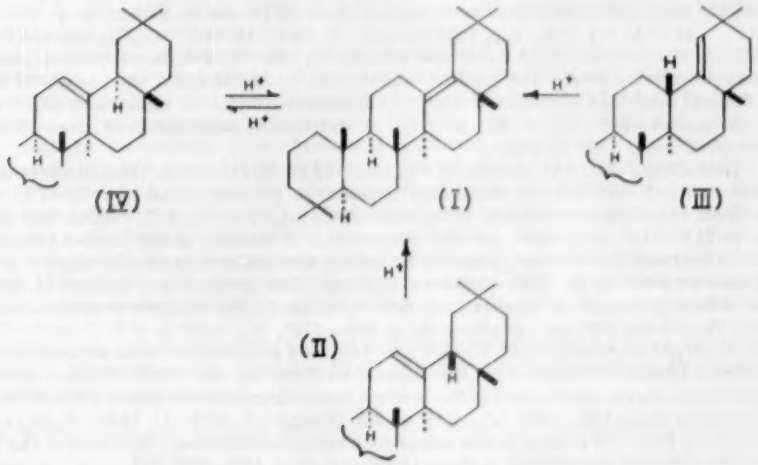
Olean-13(18)-ene, $[\alpha]_D$ −48°, is unstable to mineral acid. Treatment of the hydrocarbon with hydrochloric–acetic acid yields a mixture, $[\alpha]_D$ −12°, from which, after repeated crystallisation, a hydrocarbon, m. p. 187—188°, of constant specific rotation, $[\alpha]_D$ −20°, was isolated, and this is identical with the hydrocarbon obtained by the same treatment of olean-12-ene. With the object of identifying the hydrocarbon, $[\alpha]_D$ −20°, olean-18-ene (germanicene) (III) and 18α-olean-12-ene (IV) were prepared, the former by the recorded method[12] and the latter by oxidation of 18α-olean-12-en-3β-ol[13] with chromic acid–pyridine, followed by Wolff–Kishner reduction of the product, 18α-olean-12-en-3-one. Treatment

[7] Beaton, Spring, Stevenson, and Stewart, *J.*, 1955, 2131.
[8] Ref. *a* in Table.
[9] Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767.
[10] Ruzicka and Jeger, *ibid.*, 1941, **24**, 1236.
[11] Shaw, Spring, and Stevenson, *J.*, 1956, 465.
[12] David, *Bull. Soc. chim. France*, 1949, **16**, 427; Barton and Brooks, *J.*, 1951, 257; Halsall, Jones, and Meakins, *J.*, 1952, 2862.
[13] Allan and Spring, *J.*, 1955, 2125.

of each of the hydrocarbons (III) and (IV) with hydrochloric–acetic acid gives a mixture, repeated crystallisation of which yields the hydrocarbon, $[\alpha]_D$ −20°, identical with the product obtained by similar treatment of either olean-12-ene or olean-13(18)-ene.

18α-Olean-12-ene, $[\alpha]_D$ +37°, has m. p. 186—188° and olean-13(18)-ene, $[\alpha]_D$ −48°, has m. p. 187—188° and random mixtures of the two hydrocarbons do not show greatly depressed melting points. This suggested that the hydrocarbon, $[\alpha]_D$ −20°, m. p. 187°, is an inseparable (or difficulty separable) mixed crystal of olean-13(18)-ene (2 parts) and 18α-olean-12-ene (1 part). This view was confirmed by the preparation of a mixture of these two hydrocarbons in these proportions, a single crystallisation of which gave a hydrocarbon, m. p. 186—187°, $[\alpha]_D$ −20°, identical with that isolated from the mixtures obtained by treatment of olean-12-ene, olean-13(18)-ene, olean-18-ene, or 18α-olean-12-ene with hydrochloric–acetic acid.

These experiments show that the equilibrium mixture, $[\alpha]_D$ −10°, obtained from each of the hydrocarbons (I)—(IV) by treatment with mineral acid, is the same and contains olean-13(18)-ene and 18α-olean-12-ene. We believe that these are the only components, because a mixture of the two hydrocarbons in the ratio 4 : 3 is indistinguishable from the equilibrium mixture in its behaviour on crystallisation—the mixed crystal, $[\alpha]_D$ −20°, is obtained. Further, a mixture of equal parts of 18α-olean-12-ene, olean-13(18)-ene, and germanicene differs from the equilibrium mixture since it forms crystals, the specific rotation of which ($[\alpha]_D$ ±0°) does not change after five crystallisations. Although the mixed crystal of olean-13(18)-ene and 18α-olean-12-ene, $[\alpha]_D$ −20°, could not be isolated from the three-component mixture by crystallisation, treatment of the latter with hydrochloric–acetic acid gives the equilibrium mixture, $[\alpha]_D$ −10°, from which the mixed crystal, $[\alpha]_D$ −20°, was obtained by crystallisation. For these reasons, the behaviour of the hydrocarbons (I)—(IV) with mineral acid is represented as shown in the annexed scheme.



The mineral acid-isomerisation of simple derivatives of the hydrocarbons (I), (II), (III), and (IV) probably follows the same pattern as that established for the parents. The nature of the product obtained by crystallisation of the equilibrium mixture will depend upon the relative solubilities of the two components and upon any tendency to form insoluble mixed crystals. We have repeated the acid-isomerisation of olean-12-en-3-one (cf. Ames *et al.*[4]) and after a tedious fractional crystallisation isolated olean-13(18)-en-3-one. This specimen has a slightly lower melting point than that obtained by oxidation of olean-13(18)-en-3β-ol; like the latter preparation it gives pure olean-13(18)-ene, $[\alpha]_D$ −48° ± 2°, when reduced by the Wolff–Kishner method.

Experimental

Rotations were measured in $CHCl_3$ and ultraviolet absorption spectra in EtOH solutions. Grade II alumina and light petroleum, b. p. 60—80°, were used for chromatography.

Olean-13(18)-*en*-3β-*ol*.—A solution of oleana-11 : 13(18)-dien-3β-ol[9] (m. p. 226—228°, $[\alpha]_D$ −71°; 1·0 g.) in *cyclo*hexane (50 c.c.) and acetic acid (180 c.c.) was shaken for 16 hr. with hydrogen and platinum. The catalyst was prepared from platinum oxide (250 mg.) from which soluble salts were removed by careful washing with distilled water. The product was isolated in the usual way and crystallised from aqueous methanol, to yield olean-13(18)-en-3β-ol as needles, m. p. 212—213°, $[\alpha]_D$ −52° (*c*, 1·2). Lit. :[10,4] m. p. 213—213·5°, $[\alpha]_D$ −52°, and m. p. 212—212·5°, $[\alpha]_D$ −50·5°.

Olean-13(18)-*en*-3-*one*.—A mixture of olean-13(18)-en-3β-ol (800 mg.) in pyridine (20 c.c.) and the complex obtained by adding chromium trioxide (800 mg.) to pyridine (30 c.c.) was shaken occasionally for 16 hr., then diluted with ether, and the product was isolated in the usual way but avoiding the use of mineral acid. Purification by chromatography on alumina, followed by crystallisation from acetone–methanol gave olean-13(18)-en-3-one, as blades, m. p. 200—201°, $[\alpha]_D$ −10° (*c*, 2·3).

Oleana-11 : 13(18)-*diene*.—A mixture of oleana-11 : 13(18)-dien-3-one[11] (m. p. 236—238°, $[\alpha]_D$ −48·5°; 400 mg.), sodium methoxide (from 1·0 g. of sodium) in methanol (40 c.c.), and hydrazine hydrate (100%; 5 c.c.) was kept at 200° (autoclave) for 16 hr. The product was worked up in the usual way and crystallised from chloroform–methanol, to yield oleana-11 : 13-(18)-diene as blades, m. p. 217—218°, $[\alpha]_D$ −66° (*c*, 1·3), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 27,000, 30,000, and 20,000). A specimen prepared by oxidation of olean-12-ene with selenium dioxide[9] separated from chloroform–methanol as blades, m. p. 218—219°, $[\alpha]_D$ −65° (*c*, 0·9). Lit. :[9,1] m. p. 218—219°, $[\alpha]_D$ −73°; m. p. 222—224°, $[\alpha]_D$ −67°.

Olean-13(18)-*ene*.—(*a*) A solution of oleana-11 : 13(18)-diene (240 mg.) in *cyclo*hexane (50 c.c.) and acetic acid (150 c.c.) was shaken for 17 hr. with hydrogen and platinum (from 150 mg. of oxide). Working up in the usual way and three crystallisations of the product (m. p. 184—185°, $[\alpha]_D$ −48·5°) from chloroform–methanol yielded *olean*-13(18)-*ene* as blades, m. p. 187—188°, $[\alpha]_D$ −48°, −48·5° (*c*, 1·4, 1·2), ε_{8190} 7000 (Found : C, 88·0; H, 12·3. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%). (*b*) Olean-13(18)-en-3-one was reduced by the Wolff–Kishner method under the conditions described above. The product was worked up in the usual way, but avoiding the use of mineral acid, and crystallised from chloroform–methanol to yield olean-13(18)-ene as blades, m. p. 186—187°, $[\alpha]_D$ −48° (*c*, 1·1). A different experiment gave olean-13(18)-ene, m. p. 184—185°, $[\alpha]_D$ −50° (*c*, 2·4).

18α-*Olean*-12-*en*-3-*one*.—A solution of 18α-olean-12-en-3β-yl acetate (Budziarek *et al.*[14]) in ether was refluxed with lithium aluminium hydride, to give 18α-olean-12-en-3β-ol as fibrous needles (from chloroform–methanol), m. p. 209—210°, $[\alpha]_D$ +45° (*c*, 2·2). Allan and Spring[12] give m. p. 213—214°, $[\alpha]_D$ +50°, for this compound. A mixture of the alcohol (800 mg.) in pyridine (8 c.c.) and the complex prepared by adding chromium trioxide (800 mg.) to pyridine (8 c.c.) was kept for 18 hr. with occasional shaking. The product was isolated in the usual way but avoiding the use of mineral acid, and crystallised from chloroform–methanol to give 18α-*olean*-12-*en*-3-*one* (660 mg.) as plates, m. p. 209—210°, $[\alpha]_D$ +80° (*c*, 2·2) (Found : C, 84·5; H, 11·6. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It gives a yellow colour with tetranitromethane.

18α-*Olean*-12-*ene*.—Reduction of 18α-olean-12-en-3-one by the Wolff–Kishner method as described above, and crystallisation of the product from chloroform–methanol, yielded 18α-*olean*-12-*ene* as plates, m. p. 186—188°, $[\alpha]_D$ +37° (*c*, 3·5) (Found : C, 87·7; H, 12·3. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%). It gives a yellow colour with tetranitromethane. Mixtures of this hydrocarbon with different proportions of olean-13(18)-ene, m. p. 187—188°, $[\alpha]_D$ −48°, melted at or above 180°.

Olean-13(18)-*ene*–18α-*Olean*-12-*ene Mixture*.—(*a*) Olean-12-ene (m. p. 159—161°, $[\alpha]_D$ +94°; 300 mg.) in hot acetic acid (150 c.c.) was treated during 15 min. with concentrated hydrochloric acid (37 c.c.), and the mixture refluxed for 18 hr. and then evaporated under reduced pressure. The dried residue {$[\alpha]_D$ −10° (*c*, 3·0)} crystallised from chloroform–methanol to give blades, m. p. 181—184°, $[\alpha]_D$ −11° (*c*, 2·3). Several recrystallisations of these from the same solvent gave the crystal mixture (yield, 55%), m. p. 186—187°, $[\alpha]_D$ −18° (*c*, 2·1), further recrystallisation of which did not change the melting point or specific rotation.

(*b*) Germanicene[12] (olean-18-ene; m. p. 173—175°, $[\alpha]_D$ +6°; 150 mg.) was treated with

[14] Budziarek, Manson, and Spring, *J.*, 1951, 3336.

hydrochloric–acetic acid as described under (*a*). The total equilibrium mixture had $[\alpha]_D$ −10° (*c*, 3·0) and after three crystallisations from chloroform–methanol it gave the mixed crystal as blades (85 mg.), m. p. 186—187°, $[\alpha]_D$ −18° (*c*, 1·5), unchanged by recrystallisation.

(*c*) A solution of 18α-olean-12-ene (150 mg.) in acetic acid (120 c.c.) and concentrated hydrochloric acid (20 c.c.) was refluxed for 18 hr. After several crystallisations from chloroform–methanol, the product formed blades, m. p. 185—186°, $[\alpha]_D$ −18° (*c*, 2·3), unchanged by recrystallisation.

(*d*) The same treatment of olean-13(18)-ene, $[\alpha]_D$ −48°, gave a product which crystallised from chloroform–methanol as blades, m. p. 182—184°, $[\alpha]_D$ −12°. Three recrystallisations from the same solvent gave the mixed crystal of 18α-olean-12-ene and olean-13(18)-ene, m. p. 187—188°, $[\alpha]_D$ −19·5° (*c*, 2·3), unchanged by repeated recrystallisation.

(*e*) A mixture of olean-13(18)-ene, $[\alpha]_D$ −48° (40 mg.), and 18α-olean-12-ene (20 mg.) was crystallised from chloroform–methanol, to give blades which after recrystallisation from the same solvent had m. p. 186—187°, $[\alpha]_D$ −21° (*c*, 3·1); the m. p. and specific rotation did not change on recrystallisation.

A mixture of olean-13(18)-ene ($[\alpha]_D$ −48°; 50·4 mg.) and 18α-olean-12-ene (37·8 mg.), crystallised from chloroform–methanol, gave blades m. p. 183—186°, $[\alpha]_D$ −13°, three crystallisations of which from the same solvent gave the mixed crystal (45 mg.), m. p. 186—187°, $[\alpha]_D$ −18° (*c*, 1·5), unchanged after further crystallisation.

(*f*) A mixture of 18α-olean-12-ene (100 mg.), germanicene (100 mg.), and olean-13(18)-ene ($[\alpha]_D$ −48°, 100 mg.) was crystallised five times from chloroform–methanol during which the rotation ($[\alpha]_D$ ±1°) did not change. The mixture was reconstituted and treated with hydrochloric–acetic acid as described above. The total equilibrium mixture had $[\alpha]_D$ −10° (*c*, 2·6) and after three crystallisations from chloroform–methanol gave the mixed crystal (125 mg.) as blades, m. p. 186—187°, $[\alpha]_D$ −18° (*c*, 2·1).

The mixed crystals obtained by the methods (*a*)—(*f*) were undepressed in m. p. when mixed with each other. Treatment of the mixed crystal, $[\alpha]_D$ −19°, with hydrochloric–acetic acid, as described above, gave the equilibrium mixture which separated from chloroform–methanol as blades, m. p. 184—185°, $[\alpha]_D$ −10·4° (*c*, 1·0). Careful chromatography of the mixed crystal did not separate it into its components.

Acid Equilibration of Olean-12-en-3-one (cf. Ames *et al.*[6]). Olean-12-en-3-one (1·3 g.; m. p. 178—180°, $[\alpha]_D$ +113°) in benzene (13 c.c.) was treated with acetic acid (110 c.c.) and concentrated sulphuric acid (19·5 c.c.), and the mixture warmed to 80°, then kept for 14 days at room temperature. The separated crystalline solid {530 mg., m. p. 165—185°, $[\alpha]_D$ +2° (*c*, 1·9)} was crystallised successively from chloroform–methanol, ethanol (twice), acetone–methanol, and ethanol, to yield olean-13(18)-en-3-one as blades, m. p. 194—197° (softening at 173°), $[\alpha]_D$ −10° (*c*, 2·1). A mixture with the specimen of olean-13(18)-en-3-one, m. p. 200—201°, described above had m. p. 194—198°. The infrared spectra of the two specimens were identical; we thank Dr. G. Eglinton for making this comparison. Reduction, by the Wolff–Kishner process described above, of the specimen of olean-13(18)-en-3-one obtained by acid-isomerisation of olean-12-en-3-one, and crystallisation of the product from chloroform–methanol, gave olean-13(18)-ene as short needles, m. p. and mixed m. p. 184—185°, $[\alpha]_D$ −48° (*c*, 3·2).

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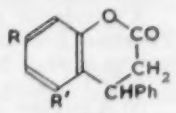
280. *The Reaction between Cinnamic Acid and Phenols in Presence of Hydrochloric Acid. A New Method for the Preparation of 3 : 4-Dihydro-4-phenylcoumarins.*

By J. D. Simpson and Henry Stephen.

Reaction between cinnamic acid and phenols in the presence of hydrochloric acid provides a new method for the preparation of 3 : 4-dihydro-4-phenylcoumarins in good yields. Crotonic acid does not react with phenols under similar conditions.

The production of 3 : 4-dihydro-4-phenylcoumarins from cinnamic acid and phenols in presence of concentrated sulphuric acid has been reported,[1] but the yields were low, probably owing to sulphonation of the products. It has now been found that phenols react readily with cinnamic acid in presence of concentrated hydrochloric acid: if the phenol has free *ortho*- and *para*-positions the product is a mixture; *e.g.*, from phenol, 3 : 4-dihydro-4-phenylcoumarin (I; R = R′ = H) and β-*p*-hydroxyphenyl-β-phenylpropionic acid are obtained; where the *para*-position is occupied the coumarin only is obtained. The yields in each case were good.



(I)

Orcinol yields the isomeric dihydrocoumarins (I; R = Me, R′ = OH; and *vice versa*). The latter was also obtained by reduction of 7-hydroxy-5-methyl-4-phenylcoumarin with sodium amalgam. No product was obtained from catechol and cinnamic acid, and phloroglucinol yielded "phloroglucid" (2 : 4 : 6 : 3′ : 5′-pentahydroxydiphenyl) by condensation of two mols. of phloroglucinol.[2] The present investigation has shown that no reaction takes place between crotonic acid and phenols in presence of hydrochloric acid.

Experimental

The following general procedure was applicable to the preparation of all coumarins. A slow stream of hydrogen chloride was passed through a boiling mixture of cinnamic acid (1 mol.), concentrated hydrochloric acid (25 c.c. per g. of cinnamic acid), and the phenol (1 mol.). The reaction was complete when the mixture became clear; the oil which separated solidified when cooled. The solid was triturated with cold sodium hydrogen carbonate solution, filtered off, washed repeatedly with cold water, dried, and crystallised from ethanol. The alkaline filtrate and washings on acidification yielded, when possible, the corresponding β-aryl-β-*p*-hydroxyphenylpropionic acid. Cinnamic acid with resorcinol monomethyl ether gives 3 : 4-dihydro-7-hydroxy-4-phenylcoumarin (7·5%) and 3 : 4-dihydro-7-methoxy-4-phenylcoumarin (87%); with resorcinol dimethyl ether it gives β-(2 : 4-dimethoxyphenyl)-β-phenylpropionic acid (76%), 3 : 4-dihydro-7-hydroxy-4-phenylcoumarin (5%), and 3 : 4-dihydro-7-methoxy-4-phenylcoumarin (11%).

Methylation of Coumarins.—(*a*) The following method [3] avoids opening the lactone ring and is applicable to the hydroxycoumarins derived from di- and tri-hydric phenols. The coumarin (1 mol.) in dry xylene was heated with powdered anhydrous potassium carbonate (2·5 mol.) and methyl sulphate (2·5 mol.) at 140° for 4 hr. with occasional shaking. The hot solution was decanted and the residue twice extracted with boiling xylene which was added to the main bulk; removal of the xylene in steam left the methylated coumarin.

(*b*) To a solution of coumarin (1 mol.) in 10% aqueous sodium hydroxide (4 mol.) at room temperature, methyl sulphate (2·5 mol.) was added in small portions with vigorous shaking. The clear solution was then heated at 80° for 30 min., cooled, and on acidification yielded the methoxy-acid. The phenylhydrazides were prepared by the action of phenylhydrazine on coumarins according to Fischer and Nouri's directions.[4] The coumarins and hydroxy-acids were acetylated by heating them with acetic anhydride and fused sodium acetate for 2 hr.

[1] Liebermann and Hartmann, *Ber.*, 1891, **24**, 2582; 1892, **25**, 957, 2130; cf Simpson and Israelstam, *J. S. African Chem. Inst.*, 1949, **2**, 165.
[2] Herzig and Pollak, *Monatsh.*, 1894, **15**, 703.
[3] Stephen and Weizmann, *J.*, 1914, **105**, 1049.
[4] Fischer and Nouri, *Ber.*, 1917, **50**, 693.

The Tables give details of compounds prepared. In addition were obtained *phenylhydrazides* from : β-*o*-hydroxyphenyl-β-phenylpropionic acid, yellow needles, m. p. 159° (Found : N, 8·4. $C_{21}H_{20}O_2N_2$ requires N, 8·4%), β-(2-hydroxy-3-methylphenyl)-β-phenylpropionic acid, yellow needles (from aqueous ethanol), m. p. 163° (Found : N, 8·2. $C_{22}H_{22}O_2N_2$ requires N, 8·1%), β-(2-hydroxy-4-methylphenyl)-β-phenylpropionic acid, needles (from aqueous methanol) (Found : N, 8·0%), β-(2-hydroxy-5-methylphenyl)-β-phenylpropionic acid, needles (from aqueous

Substituted 3 : 4-*dihydro*-4-*phenylcoumarins.*

Subst.	Yield (%)	M. p.	Form	Solvent	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
—[a]	53	83°	Plates	Aq. EtOH	80·3	5·4	$C_{15}H_{12}O_2$	80·4	5·4
8-Me[a]	64	106	Needles	,,	80·6	5·9	$C_{16}H_{14}O_2$	80·6	5·9
7-Me[a]	46	121	,,	,,	80·7	6·0			
6-Me[a]	—	83	,,	,,	80·6	6·0			
7 : 8-Benzo[a]	74	111·5	,,[b]	MeOH	83·0	5·1	$C_{19}H_{14}O_2$	83·2	5·1
5 : 6-Benzo[a]	98	115	,,[b]	EtOH	83·1	5·1			
7-OH[a]	99	140	,,	Aq. EtOH	74·9	5·3	$C_{15}H_{12}O_2$	75·0	5·0
7-OMe	87	112	,,	Aq. MeOH	75·6	5·7	$C_{16}H_{14}O_2$	75·5	5·5
7-OAc	—	89	Cubes	Aq. MeOH	72·3	5·1	$C_{17}H_{14}O_4$	72·3	5·0
7-OBz[d]	—	153	Needles	MeOH	73·05	5·4	$C_{22}H_{16}O_4,H_2O$	72·9	5·4
	—	122	,,	C_6H_6	76·7	4·8	$C_{22}H_{16}O_4$	76·7	4·7
6-OH[a]	98	133	,,	Aq. EtOH	75·1	5·2	$C_{15}H_{12}O_2$	75·0	5·0
6-OMe	—	108	Cubes	MeOH	75·5	5·5	$C_{16}H_{14}O_2$	75·6	5·5
6-OAc	—	93	,,	EtOH	72·3	5·1	$C_{17}H_{14}O_4$	72·3	5·0
5-OH-7-Me[a]	87	218	,,	MeOH	75·5	5·6	$C_{16}H_{14}O_2$	75·6	5·5
7-OH-5-Me[a]	7·5	163	Needles	50% MeOH	75·6	5·7			
5-OMe-7-Me	—	147	,,	MeOH	76·1	6·1	$C_{17}H_{16}O_2$	76·1	6·0
5-OAc-7-Me	—	160	,,	,,	72·9	5·5	$C_{18}H_{16}O_4$	73·0	5·4
7 : 8-$(OH)_2$	98	147	,,	Aq. EtOH	70·1	4·8	$C_{15}H_{12}O_4$	70·3	4·7
7 : 8-$(OMe)_2$	—	112	,,	,,	67·6	6·0	$C_{17}H_{16}O_4,H_2O$	67·5	6·0
7 : 8-$(OAc)_2$	—	168	,,	EtOH	66·9	4·7	$C_{19}H_{16}O_6$	67·0	4·7
7 : 8-$(OH)_2$-5-CO_2H	96	248[f]	,,	EtOH	63·9	4·0	$C_{16}H_{12}O_6$	64·0	4·0
7 : 8-$(OMe)_2$-5-CO_2Me[g]	—	191	Cubes	MeOH	66·6	5·4	$C_{19}H_{18}O_6$	66·6	5·4
7 : 8-$(OAc)_2$-5-CO_2H[h]	—	243	—	MeOH	62·5	4·2	$C_{20}H_{16}O_8$	62·5	4·2
7-OH-3-Ph	52	175	Needles	Aq. MeOH	79·7	5·1	$C_{21}H_{16}O_3$	79·6	5·1
7-OMe-3-Ph	—	83	—	—	80·0	5·6	$C_{22}H_{18}O_3$	80·0	5·5

[a] For previous preparations see ref. 1. [b] Yellow; others are colourless. [c] For previous preparation see Koelsch, *J. Amer. Chem. Soc.*, **1936**, **58**, 1326. [d] Prepared by the Schotten–Baumann method. [e] Obtained from orcinol as a mixture, separated by dissolution in the minimum amount of methanol, from which the main component separated; the minor component was obtained on dilution of the mother-liquor with water. [f] Decomp.; blue colour with aqueous $FeCl_3$. [g] Prepared by methyl sulphate and potassium carbonate in xylene. [h] Ag *salt* : Found : Ag, 21·7; Reqd. : Ag, 21·9%.

β-*Aryl*-β-*phenylpropionic acids.*

Aryl	M. p.	Form	Solvent	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H	Ag (%) in Ag salt Found	Ag (%) in Ag salt Reqd.
Ph[a, b, 1]	153[2]	Needles	Aq. EtOH	74·3	5·9	$C_{15}H_{14}O_2$	74·4	5·8	30·7	30·4
o-MeO·C_6H_4[a]	135	,,	,,	75·1	6·4	$C_{16}H_{16}O_2$	75·0	6·3	29·4	29·7
p-MeO·C_6H_4[a]	123	,,	MeOH	74·9	6·2				29·6	
p-AcO·C_6H_4	125	Cubes	Aq. EtOH	71·8	5·7	$C_{17}H_{16}O_4$	71·8	5·7	27·4	27·6
4 : 3-HO·C_6H_3Me[b, 2]	96	Needles	H_2O	75·0	6·3	$C_{16}H_{16}O_2$	75·0	6·3	29·6	29·7
2 : 3-MeO·C_6H_3Me	127	Plates	MeOH	75·5	6·7	$C_{17}H_{18}O_2$	75·5	6·7	28·8	28·6
4 : 3-MeO·C_6H_3Me	120	Needles	Aq. MeOH	75·6	6·7				28·4	
4 : 3-AcO·C_6H_3Me	98	,,	Aq. AcOH	72·5	6·1	$C_{18}H_{18}O_4$	72·5	6·0	26·5	26·6
4 : 2-HO·C_6H_3Me[b, 3]	126	,,	Aq. EtOH	75·0	6·4	$C_{16}H_{16}O_2$	75·0	6·3	29·8	29·7
2 : 4-MeO·C_6H_3Me	133	Plates	MeOH	75·5	6·7	$C_{17}H_{18}O_2$	75·5	6·7	28·4	28·6
4 : 2-MeO·C_6H_3Me	121	Cubes	Aq. MeOH	75·5	6·8				—	
4 : 2-AcO·C_6H_3Me	90	Needles	Aq. AcOH	72·4	6·1	$C_{18}H_{18}O_4$	72·5	6·1	26·6	26·6
2 : 5-MeO·C_6H_3Me	132	Cubes	Aq. EtOH	75·4	6·8	$C_{17}H_{18}O_2$	75·5	6·7	28·8	28·6
4 : 1-HO·$C_{10}H_6$[4]	171	Needles[c]	—	77·9	5·6	$C_{19}H_{16}O_2$	78·8	5·5	—	—
1 : 2-MeO·$C_{10}H_6$[e]	114·5	Needles	EtOH	78·3	5·9	$C_{20}H_{18}O_2$	78·4	5·9	—	—
4 : 1-AcO·$C_{10}H_6$	93	Needles[c]	,,	75·4	5·5	$C_{21}H_{18}O_4$	75·4	5·5	—	—
2 : 1-MeO·$C_{10}H_6$[d]	170	,,	Aq. MeOH	78·4	5·9	$C_{20}H_{18}O_2$	78·4	5·9	26·0	26·1
2 : 4-$(MeO)_2C_6H_3$[c, 5]	123	,,	,,	71·4	6·6	$C_{17}H_{18}O_4$	71·3	6·3	27·3	27·4
2 : 5-$(MeO)_2C_6H_3$	127	,,	,,	71·2	6·2				27·3	

[a] For previous preparations see ref. 1. [b] No colour with $FeCl_3$. [c] Yellow; others are colourless. [d] As footnote *c* to previous Table. [e] Also obtained by methylating 3 : 4-dihydro-7-hydroxy-4-methylcoumarin in alkali.

Yields : [1] 45, [2] 34, [3] 52, [4] 10, [5] 76%.

ethanol), m. p. 173° (decomp.) (Found: N, 8·2%), and β-(2-hydroxy-1-naphthyl)-β-phenylpropionic acid, cubes (from dilute methanol), m. p. 148° (Found: N, 7·2. $C_{25}H_{22}O_2N_2$ requires N, 7·3%).

β-(2-Hydroxy-5-methylphenyl)-β-phenylpropionamide was obtained by saturating a solution of 3 : 4-dihydro-4-phenyl-6-methylcoumarin (2 g.) in methanol (20 c.c.) at −5° with ammonia, heating the solution in a pressure vessel at 80° for 4 hr., and removing the solvent and excess of ammonia in a vacuum. The residue crystallised from methanol containing ammonia, as needles, m. p. 162° (decomp.) (Found: N, 5·5. $C_{16}H_{17}O_2N$ requires N, 5·5%).

Methyl-β-(2 : 4-dimethoxyphenyl)-β-phenylpropionate was obtained by saturating a solution of β-(2 : 4-dimethoxyphenyl)-β-phenylpropionic acid (1 g.) in methanol (10 c.c.) at 0° with hydrogen chloride; after 12 hr. at 0°, the solution was boiled for 1 hr., and the methanol distilled off, leaving the ester which solidified in ice. Crystallisation from aqueous methanol gave needles, m. p. 75° (Found: C, 72·0; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

We are indebted to Mr. A. Greig-Gass for a specimen of 7-hydroxy-5-methyl-4-phenylcoumarin.

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281. *The Chemistry of Extractives from Hardwoods. Part XXVI.* Experiments on cyclo*Eucalenol, *a New Triterpene from* Eucalyptus microcorys.

By J. S. G. COX, F. E. KING, and T. J. KING.

A new triterpene has been obtained by saponification of the oily light-petroleum extract of tallow wood (*Eucalyptus microcorys*, fam. *Myrtaceae*), which, bearing a general similarity to the *cyclo*artenol sub-group, has been named *cyclo*eucalenol.

*cyclo*Eucalenol is a monohydric secondary alcohol, apparently $C_{31}H_{52}O$. It contains one ethylenic bond, present in a side chain terminated by the grouping $-CH_2{\cdot}C(:CH_2){\cdot}CHMe_2$. The occurrence of a *cyclo*propane ring was revealed by the action of hydrogen chloride and by the infrared absorption at 3050 cm.$^{-1}$. Oxidation of the unsaturated acid-isomerisation products from demethyl*cyclo*eucalanyl acetate, a dihydro-derivative having the modified terminal group $-CH_2{\cdot}CH_2{\cdot}CHMe_2$, gave a diketone containing the transoid system $-CO{\cdot}\overset{|}{C}{=}\overset{|}{C}{\cdot}CO-$ but not identical with 7 : 11-dioxolanost-8-enyl acetate.

OF the various Australian timbers available commercially in the United Kingdom, several noted for their very high durability, *e.g.*, jarrah, spotted gum, are derived from *Eucalyptus* species. From several published reports [1] it may be inferred that ellagic acid is a common constituent of *Eucalyptus* woods, and we have isolated this acid from two or three varieties by extraction with alcohol, but no examination of the extractive constituents of these woods appears to have been recorded. *Eucalyptus microcorys* has been the subject of our first investigation in this group, in part because of the oily nature of this timber which is indicated by its common description as tallow wood.

Treatment with boiling light petroleum sufficed to remove the oily components and, when the resulting amber syrup was saponified, an alkali-insoluble material remained which when purified by chromatography gave a highly crystalline solid, m. p. 140°, amounting to 0·7% of the original wood. More detailed examination of this product has shown that it belongs to the *cyclo*artenol sub-group of triterpenes, whence it has been named *cyclo*eucalenol. It is remarkable that shortly afterwards *cyclo*eucalenol was again isolated in

* Part XXV, *J.*, 1955, 2948.

[1] Wade, *Pharm. J.*, 1925, **115**, 131; Anderson and Steedor, *J. Soc. Leather Trades' Chemists*, 1950, **34**, 478; Hillis, *Austral. J. Sci. Res.*, 1952, *A*, **5**, 379; M. M. Chattaway, *Austral. J. Bot.*, 1953, **1**, 27.

our laboratory, by Mr. J. M. Uprichard, from the heartwood of *Erythrophloeum guineense* (fam. *Leguminoseae*), a circumstance which may imply a wide distribution of this hitherto unknown natural product.

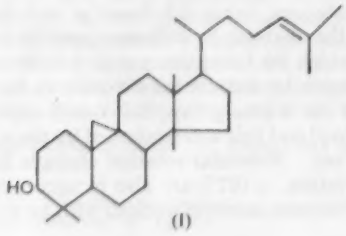
Analyses of *cyclo*eucalenol were in agreement with the formula $C_{30}H_{50-52}O$, but did not exclude $C_{31}H_{50-52}O$, and similarly for the various derivatives, *i.e.*, acetate, benzoate, 3 : 5-dinitrobenzoate, and α-naphthylurethane, by which the oxygen function was demonstrated. The alcoholic group was oxidised either with chromic oxide–acetic acid or chromic oxide–pyridine,[2] the product, *cyclo*eucalenone, being a ketone, as was shown by the light absorption maximum (368 mμ) of the derived 2 : 4-dinitrophenylhydrazone.[3] The ketone reacted to the Zimmermann test, which for triterpene nuclei is believed to be typical of the 3-oxo-group,[4] and was reduced again by sodium borohydride to the parent alcohol. In view of the unhindered nature of the 3-keto-group, this result appeared to denote an equatorial conformation for the hydroxyl and this was confirmed by the existence of a peak at 1040 cm.$^{-1}$ in the infrared spectrum. Molecular-rotation changes following acylation (Δ_1, acetylation, +106°; Δ_2, benzoylation, +167°) are also in agreement with those of a 3β(equatorial)-hydroxyl group in a triterpene or sterol nucleus with an A : B *trans* ring system.

The presence of a double bond in *cyclo*eucalenol, apparent colorimetrically (tetranitromethane), was confirmed by catalytic hydrogenation of the acetate to a dihydro-derivative, *cyclo*eucalanyl acetate, which was shown to be saturated by its stability to peracetic acid and by the absence of appreciable absorption at 200—220 mμ. *cyclo*Eucalanol was prepared by hydrolysis of the acetate and oxidised by chromic oxide–pyridine to *cyclo*eucalanone. The ketone was characterised by the usual derivatives, and when reduced by the Wolff–Kishner method afforded the saturated hydrocarbon *cyclo*eucalane.

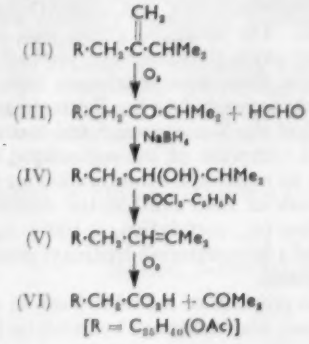
From ultraviolet end absorption measurements the *cyclo*eucalenol ethylene bond appeared to be disubstituted.[5] Ozonolysis, which resulted in the liberation of formaldehyde—isolated as 2 : 4-dinitrophenylhydrazone and dimedone derivatives—proved the centre of unsaturation to be a vinylidene group, and the existence of infrared absorption bands at 889 and 1640 cm.$^{-1}$ gave independent support to this. Absorption due to unsaturation was absent also from the infrared spectrum of the dihydro-compound, *cyclo*eucalanyl acetate, but a shoulder was observed at *ca* 3050 cm.$^{-1}$, thus affording the first indication of the *cyclo*propane ring[6] afterwards found by chemical methods to be a characteristic feature of the molecule. The hydrocarbon *cyclo*eucalane which was prepared in the course of these experiments also exhibits absorption at 1010 cm.$^{-1}$ sometimes associated with a *cyclo*propane ring.[6] The features disclosed by this preliminary survey of *cyclo*eucalenol enabled it to be formulated as a pentacyclic, monohydroxy-, monoethylenic triterpene, and its many points of resemblance to *cyclo*artenol[7] (I) seemed at first to imply a close structural relationship between the two compounds. Further experiments, however, disclosed important differences. For example, an examination of the volatile fraction from the ozonolysis of *cyclo*eucalenyl acetate (II), by chromatography of the crude 2 : 4-dinitrophenylhydrazone,[8] revealed no trace of acetone such as is formed from the terminal group of the *cyclo*artenol side chain. An explanation of this divergency was found in the further degradation of the principal ozonolysis product of *cyclo*eucalenyl acetate, which at low temperatures consisted of a crystalline ketone, demethyloxo*cyclo*eucalanyl acetate (III). The ketone, which from the Zimmermann reaction appeared to contain a $-CO\cdot CH_2-$ group, was first reduced by sodium borohydride to the corresponding alcohol (IV), and the latter was then dehydrated with phosphoryl chloride in pyridine. The product (V), though it did not give satisfactory analyses, had a strong tetranitromethane reaction, and its ultraviolet absorption was indicative of a trisubstituted double bond. Ozonolysis of this olefin gave acetone and an acid (VI), characterised by its methyl ester, to which the

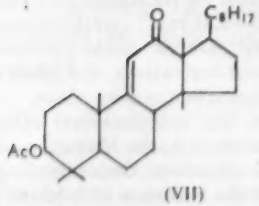
[2] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[3] Braude and Jones, *J.*, 1945, 498.
[4] Barton and de Mayo, *J.*, 1954, 887.
[5] Bladon, Henbest, and Wood, *J.*, 1952, 2737.
[6] Cole, *Chem. and Ind.*, 1953, 946; *J.*, 1954, 3807.
[7] Barton, Page, and Warnhoff, *J.*, 1954, 2715; Irvine, Henry, and Spring, *J.*, 1955, 1316.
[8] Meigh, *Nature*, 1952, **170**, 579.

formula $C_{26}H_{42}(OAc)\cdot CO_2H$ is assigned. These reactions, illustrated in the accompanying diagram, not only enable the terminal unit of the side chain to be identified as $-CH_2\cdot C(:CH_2)\cdot CHMe_2$ but, by analogy with eburicoic acid,[9] euphorbol,[10] and *cyclo*laudenol,[11] imply that the complete substituent is $-CHMe\cdot CH_2\cdot CH_2\cdot C(:CH_2)\cdot CHMe_2$ thereby adding further support to the C_{31} formula.

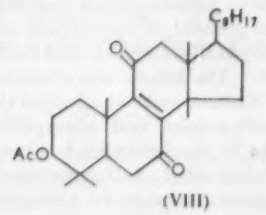


(I)





(VII)



(VIII)

Confirmation for the *cyclo*propane ring was obtained as with *cyclo*artenol by the action of hydrogen chloride on *cyclo*eucalanyl acetate, whereupon isomerisation occurred with the formation of a mixed product showing marked short-wave ultraviolet absorption and olefinic bands in the infrared spectrum. Repeated crystallisation of a sample afforded a small yield of a seemingly pure compound (eucalenyl acetate) $C_{31}H_{53}OAc$, having ultraviolet absorption indicative of a trisubstituted double bond. Following the procedure developed by Bentley, Henry, Irvine, and Spring for the investigation of *cyclo*artenol,[12] the crude mixture was oxidised with chromic oxide in acetic acid and the resulting material fractionated by chromatography. In addition to unchanged eucalenyl acetate, two further products were isolated, one an unsaturated ketone (acetate) $C_{31}H_{51}O\cdot OAc$ with $\alpha\beta$-ethylenic absorption, and the other a pale yellow compound $C_{31}H_{49}O_2\cdot OAc$. For convenience the unsaturated ketone is at present designated oxoeucalenyl acetate although it does not follow that the position of the double bond is identical with that on eucalenyl acetate or that the enone system is necessarily situated as in the corresponding *cyclo*artenol derivative (VII). On the other hand, there is little doubt that the compound $C_{31}H_{49}O_2\cdot OAc$, which has the characteristic ultraviolet light absorption of a transoid enedione, is closely related to 7 : 11-dioxolanost-8-enyl acetate (VIII) obtained by the oxidation of certain triterpenes unsaturated at the 7 : 8- or 8 : 9-position,[13] including the isomerised *cyclo*artenyl acetate. The dioxoeucalenyl acetate was hydrolysed to the parent alcohol, and

[9] Gascoigne, Holker, Ralph, and Robertson, *J.*, 1951, 2346; Holker, Powell, Robertson, Simes, Wright, and Gascoigne, *J.*, 1953, 2414, 2422.

[10] Arigoni, Wyler, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 1553; Arigoni, Jeger, and Ruzicka, *ibid.*, 1955, **38**, 222; Barbour, Warren, and Wood, *J.*, 1951, 2537; Christian, Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 510; Barbour, Lourens, Warren, and Watling, *J.*, 1955, 2194.

[11] Bentley, Henry, Irvine, Mukerji, and Spring, *J.*, 1955, 596; Henry, Irvine, and Spring, *ibid.*, p. 1607.

[12] Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673.

[13] *Inter alia* Ruzicka, Ray, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; Dorée and McGhie, *Nature*, 1954, **173**, 148; Dorée and Kurzer, *J.*, 1948, 988; 1949, 570; Lahey and Strasser, *J.*, 1951, 873.

as in the case of the diketone (VIII) was reduced with zinc–acetic acid to the saturated dione. Oxidation of eucalenyl acetate with chromic oxide in acetic acid also gave oxoeucalenyl acetate, identical (mixed m. p.) with that obtained from the acid-isomerisation product of *cyclo*eucalanyl acetate. Eucalanyl acetate, and thence eucalanol, was obtained by vigorous catalytic reduction of eucalenyl acetate, from which an epoxide was also prepared.

From the general structural similarity of *cyclo*eucalenol and *cyclo*artenol apparent in the foregoing reactions it seemed possible that after elimination of the obvious difference due to the additional carbon atom at position 24, a derivative common to the two compounds might be obtained, which would thus establish the remaining structural features of the new alcohol. In the first attempt to relate the two triterpenes in this way, demethyloxo-*cyclo*eucalanol was reduced by the Wolff–Kishner method to demethyl*cyclo*eucalanol, characterised by its acetate, when it became obvious that the reduction product was not identical with *cyclo*artanol. Accordingly, the effect of eliminating the *cyclo*propane ring was next investigated, using for this purpose the newly prepared demethyl*cyclo*eucalanol. Isomerisation of the acetate with hydrogen chloride, as outlined for the higher homologue, gave a mixture which, when oxidised, yielded the expected products, *viz.*, demethyleucalenyl acetate and demethyloxo- and -dioxo-eucalenyl acetate. However, a comparison of the dioxo-compound with 7 : 11-dioxolanost-8-enyl acetate, which caused a large melting-point depression, indicated their dissimilarity.

The failure of these experiments to relate *cyclo*eucalenol to known triterpene compounds may be due to one or more causes. In the first place, although the transformations recorded are compatible with the occurrence of the methylene bridge (*cyclo*propane ring) at the 9 : 10-position, as in *cyclo*artenol, a significant difference is observed between the alteration of optical rotatory power which follows the oxidation of *cyclo*eucalenol to *cyclo*eucalenone (positive shift) and that which occurs in passing from *cyclo*artenol to *cyclo*artenone (negative shift). It has been suggested[14] that in the case of *cyclo*artenol the (exceptional) negative change is occasioned by the β-conformation of the substituent (CH_2) at $C_{(9)}$. If this inference is valid and the 9-position in *cyclo*eucalenol is involved in a *cyclo*propane ring, it would accordingly imply that the methylene bridge is linked with $C_{(11)}$, as was formerly proposed for *cyclo*artenol. The possible union of other carbon atoms, giving an alternative site for the *cyclo*propane ring cannot be excluded at this stage. However, the non-identity of dioxodemethyleucalenyl acetate and the dioxolanostenyl acetate (VIII) shows that, apart from any lack of correspondence with respect to the *cyclo*propane unit, at least one further point of dissimilarity exists with respect to *cyclo*artenol. It is probable that the difference is one of configuration, possibly at position 17 and/or 20, as already postulated, for example, or euphol. It is unlikely that the angular methyl groups attached to $C_{(13)}$ and $C_{(14)}$ have the euphol configuration[15] since no derivative corresponding to the hypothetical *iso*eucalenol series has been detected among the acid-isomerisation products of *cyclo*eucalenol and its compounds. Further experiments designed to elucidate the undetermined structural or stereochemical features of *cyclo*eucalenol are in progress.

Experimental

Specific rotations were measured with $CHCl_3$ solutions at room temperature, and ultraviolet absorption spectra with EtOH and a Unicam S.P.500 Spectrophotometer. Light petroleum refers to the fraction of b. p 60—80° unless otherwise specified.

Extraction of Eucalyptus microcorys *with Light Petroleum.*—The finely shredded heartwood (3·95 kg.) was extracted with boiling light petroleum for 24 hr., evaporation of the solution leaving a clear amber syrup (90 g., 2·33%). This was redissolved in light petroleum (300 c.c.), and after filtration from gelatinous solid (5·2 g., 0·13%), the solution was evaporated and the residual oil (85 g.) heated under reflux for 4 hr., with a 25% solution of potassium hydroxide in aqueous ethanol (800 c.c., 85% ethanol). The non-saponifiable fraction (47 g.) was isolated with ether in the usual manner as a semicrystalline solid (47 g.) which was dissolved in benzene (250 c.c.) and percolated through a column (43 × 4·5 cm.) of alumina (600 g.), the chromatogram

[14] Dawson, Halsall, Jones, Meakins, and Phillips, *Chem. and Ind.*, 1955, 918.
[15] Barton, McGhie, Pradhan, and Knight, *J.*, 1955, 876.

being eluted with (*a*) benzene (2 l.), (*b*) benzene–ether (9 : 1; 3 l.), (*c*) benzene–ether (4 : 1; 2 l.), (*d*) benzene–ether (1 : 1; 3 l.), and (*e*) ether (3 l.). Evaporation of the combined fractions (*b*) and (*c*) left a pale yellow solid (28·5 g.) which when crystallised from light petroleum or ethyl acetate gave cyclo*eucalenol* as colourless feathery needles, $[\alpha]_D$ +45° (*c*, 2·9), m. p. 138—139°, raised to 140° after drying for 3 hr. *in vacuo* at 100° (Found in a specimen dried above the m.p.: C, 84·2, 84·0; H, 11·4, 11·8. $C_{31}H_{52}O$ requires C, 84·5; H, 11·9%).

*cyclo*Eucalenol gives a pale yellow colour with tetranitromethane. In the Liebermann–Burchard test it forms a brown solution with a strong green fluorescence. Treatment of the terpene (500 mg.) with acetic anhydride (10 c.c.) and pyridine (20 c.c.) for 24 hr. at room temperature gave cyclo*eucalenyl acetate*, which separated from chloroform–methanol as blades, $[\alpha]_D$ +63° (*c*, 1·54), m. p. 110° (Found: C, 81·9; H, 11·5. $C_{33}H_{54}O_2$ requires C, 82·1; H, 11·3%); light absorption: $\varepsilon_{310} = 1048$, $\varepsilon_{220} = 261$, $\varepsilon_{310}/\varepsilon_{220} = 4·01$. Infrared bands in CS_2: 3050 (sh.), 1640, and 889 cm.$^{-1}$. The *benzoate*, prepared from *cyclo*eucalenol (500 mg.) in pyridine (5 c.c.) under reflux with benzoyl chloride (2 c.c.) for 2 hr., crystallised from ethyl acetate as needles, $[\alpha]_D$ +67° (*c*, 0·9), m. p. 130° (Found: C, 83·7; H, 10·5. $C_{38}H_{56}O_2$ requires C, 83·8; H, 10·4%). The 3 : 5-*dinitrobenzoate*, prepared similarly, crystallised from light petroleum as needles, m. p. 205° (Found: C, 71·9; H, 8·31; N, 4·5. $C_{45}H_{64}O_6N_2$ requires C, 71·9; H, 8·6; N, 4·5%). The *α-naphthylurethane* formed plates (from ethanol), m. p. 176° [Found: C, 82·6; H, 9·5%; *M* (Rast), 548. $C_{42}H_{59}O_2N$ requires C, 82·7; H, 9·75%; *M*, 609].

In later experiments the isolation of *cyclo*eucalenol was carried out *via* the acetate prepared from the crude unsaponifiable material (47 g.), with acetic anhydride (200 c.c.) and pyridine (300 c.c.) at room temperature for 48 hr. The crude product (50 g.), isolated by means of ether, was chromatographed in light petroleum (200 c.c.) on alumina (1200 g.; 82·0 × 4·5 cm.), the column being eluted with (*a*) light petroleum (5 l.), (*b*) light petroleum–benzene (4 : 1; 4 l.), (*c*) light petroleum–benzene (1 : 1; 3 l.), and (*d*) benzene (2 l.). Evaporation of fraction (*a*) gave a colourless solid (33 g.) which crystallised from chloroform–methanol as needles, m. p. 109—110°, consisting of *cyclo*eucalenyl acetate identical with that obtained from pure *cyclo*eucalenol. A further quantity (5 g.) was obtained by evaporation of the combined fractions (*b*) and (*c*).

Isolation of a Sterol Fraction.—Evaporation of chromatogram fraction (*e*) from the crude unsaponifiable matter gave a colourless solid (1·8 g.) which crystallised from methanol as needles, m. p. 138—139°, raised to 140° after repeated recrystallisation from light petroleum (Found: C, 84·0; H, 12·1. $C_{29}H_{50}O$ requires C, 84·0; H, 12·2%), $[\alpha]_D$ −5° (*c*, 1·1); light absorption: $\varepsilon_{310} = 2490$, $\varepsilon_{220} = 556$; $\varepsilon_{310}/\varepsilon_{220} = 4·48$. In the Liebermann–Burchard test this sterol underwent the colour changes, pink ⟶ purple ⟶ blue ⟶ green. No fluorescence was observed. It gave a yellow colour with tetranitromethane and a positive Tortelli–Jaffe reaction indicative of the presence of a double bond at $C_{(8)}$. The *sterol acetate* separated from chloroform–methanol as needles, $[\alpha]_D$ −10° (*c*, 1·0), m. p. 118—119° (Found: C, 81·3; H, 11·2. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·4%). The *benzoate* crystallised from chloroform–methanol in plates, $[\alpha]_D$ +15° (*c*, 0·8), m. p. 135—136° (Found: C, 83·5; H, 10·2. $C_{36}H_{54}O_2$ requires C, 83·3; H, 10·5%). The 3 : 5-*dinitrobenzoate*, very pale yellow needles (from light petroleum), had m. p. 195—196° (Found: C, 71·0; H, 8·4. $C_{36}H_{52}O_6N_2$ requires C, 71·0; H, 8·6%).

cyclo*Eucalenone*.—(i) A solution of *cyclo*eucalenol (1 g.) in pyridine (10 c.c.) was added at room temperature, during 30 min., to a slurry of chromic oxide (1 g.) in pyridine (10 c.c.) prepared as by Poos, Arth, Beyler, and Sarett.[1] After 24 hr. the neutral product was isolated with ether and crystallised from ethanol, to yield cyclo*eucalenone* as needles (780 mg.), $[\alpha]_D$ +54° (*c*, 0·8), m. p. 84° (Found: C, 84·6; H, 11·4 $C_{31}H_{50}O$ requires C, 84·9; H, 11·3%).

(ii) A solution of *cyclo*eucalenol (1 g.) in acetic acid (200 c.c.) was treated at room temperature with chromic oxide (200 mg.) in acetic acid (50 c.c.) during 30 min. After 12 hr., the neutral product was isolated in the usual manner, and yielded *cyclo*eucalenone as needles (820 mg.) (from ethanol), m. p. and mixed m. p. 84°.

cyclo*Eucalenone oxime* separated as needles (from light petroleum), m. p. 176—177° (Found: C, 82·1; H, 11·3. $C_{31}H_{51}ON$ requires C, 82·1; H, 11·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from xylene–ethanol in needles, m. p. 246° (Found: C, 71·9; H, 8·7; N, 9·35. $C_{37}H_{55}O_4N_4$ requires C, 71·8; H, 8·8; N, 9·1%); light absorption in $CHCl_3$: $\lambda_{max.}$ 368 mμ (ε 24,000).

*cyclo*Eucalenone (300 mg.) in methanol (35 c.c.) with sodium borohydride (100 mg.) in methanol (20 c.c.) at room temperature for 24 hr. gave *cyclo*eucalenol (250 mg.); the product, isolated in the usual way, crystallised from light petroleum as needles, m. p. and mixed m. p. 138—139°.

cyclo*Eucalanyl Acetate.*—*cyclo*Eucalenyl acetate (2 g.) in acetic acid (100 c.c.) was shaken with hydrogen and platinum (from 150 mg. of platinum oxide) for 45 min.; the uptake of hydrogen being 97 c.c. at N.T.P. (theor. for 1 double bond, 95·7 c.c.). Crystallised from chloroform–methanol, the resultant cyclo*eucalanyl acetate* formed needles (1·85 g.), $[\alpha]_D$ +62° (*c* 0·6), m. p. 112—113° (Found: C, 82·0; H, 11·9. $C_{32}H_{56}O_2$ requires C, 81·8; H, 11·6%). It gave a pale yellow colour with tetranitromethane and showed very weak light absorption between 200 and 225 mμ, $\varepsilon_{210} = 284$, $\varepsilon_{220} = 108$, $\varepsilon_{210}/\varepsilon_{220} = 2·62$. It was almost quantitatively recovered on treatment with a 10-fold excess of monoperphthalic acid at 0° for 14 days and with perhydrol–acetic acid on the steam-bath for 2 hr.

cyclo*Eucalanol.*—Hydrolysis of *cyclo*eucalanyl acetate with 5% ethanolic potassium hydroxide solution gave cyclo*eucalanol*, which separated from methanol as plates, $[\alpha]_D$ +52° (*c* 0·7), m. p. 149—150° (Found: C, 84·2; H, 12·1. $C_{31}H_{54}O$ requires C, 84·1; H, 12·3%); light absorption: $\varepsilon_{210} = 235$, $\varepsilon_{220} = 31$, $\varepsilon_{210}/\varepsilon_{220} = 7·52$.

cyclo*Eucalanyl benzoate* separated from ethyl acetate as needles, $[\alpha]_D$ +64° (*c* 0·64), m. p. 130° (Found: C, 83·3; H, 10·4. $C_{38}H_{58}O_2$ requires C, 83·5; H, 10·7%).

cyclo*Eucalanone.*—Oxidation of *cyclo*eucalanol (500 mg.) with chromic acid (500 mg.) in pyridine (10 c.c.) for 24 hr. at room temperature and isolation of the product with ether gave cyclo*eucalanone* (400 mg.) as plates (from ethanol), $[\alpha]_D$ +49° (*c* 0·9), m. p. 107—108° (Found: C, 84·2; H, 11·7. $C_{31}H_{52}O$ requires C, 84·5; H, 11·9%); light absorption: $\lambda_{max.}$ 280 mμ (ε 35). The *oxime*, needles from ethanol, had m. p. 191—192° (Found: C, 81·6; H, 12·1; N, 3·4. $C_{31}H_{53}ON$ requires C, 81·5; H, 11·7; N, 3·1%). The *semicarbazone* crystallised from ethanol in needles, m. p. 210° (Found: C, 77·4; H, 11·4; N, 8·8. $C_{32}H_{55}ON_3$ requires C, 77·2; H, 11·4; N, 8·4%); light absorption: $\lambda_{max.}$ 229 mμ (ε 16,200). The 2:4-*dinitrophenylhydrazone* separated from ethanol–xylene in plates, m. p. 247° (Found: C, 71·4; H, 9·0; N, 9·3. $C_{37}H_{56}O_4N_4$ requires C, 71·6; H, 9·1; N, 9·0%); light absorption: $\lambda_{max.}$ 368 mμ (ε 24,000).

cyclo*Eucalanane.*—*cyclo*Eucalanone (500 mg.) in anhydrous hydrazine (5 c.c.) and ethanol (20 c.c.) containing dissolved sodium (630 mg.) was heated at 180° for 48 hr. The product, worked up in the normal way, was purified by chromatography in light petroleum on alumina, thus giving cyclo*eucalanane* (420 mg.) which separated from chloroform–methanol as needles, $[\alpha]_D$ +25° (*c* 0·5), m. p. 58—59° (Found: C, 87·3; H, 12·4. $C_{31}H_{54}$ requires C, 87·3; H, 12·7%).

Oxidation of cyclo*Eucalenyl Acetate.*—(i) *By ozonolysis.* *cyclo*Eucalenyl acetate (2 g.) in methylene dichloride (60 c.c.) was treated at −45° with ozonised oxygen (5—7%) for 1 hr. After attaining room temperature, the solution was treated with acetic acid (15 c.c.) and portionwise with zinc dust (4 g.) during 30 min. After 1 hour's stirring, the filtered solution was washed, and the aqueous washings were adjusted to pH 7·0 and treated with saturated aqueous dimedone (150 c.c.). Formaldehyde–dimedone (0·37 g., 30%) was obtained as needles (from ethanol), m. p. and mixed m. p. 189—190°. Evaporation of the dried methylene dichloride solution gave *demethyloxo*cyclo*eucalanyl acetate* (1·8 g.), which crystallised from methanol in needles, $[\alpha]_D$ +35° (*c* 0·6), m. p. 97—98° (Found: C, 79·4; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%); light absorption: $\lambda_{max.}$ 282 mμ (ε 43).

*cyclo*Eucalenyl acetate (3 g.) was also ozonised at 0° in dry carbon tetrachloride (60 c.c.) for 2 hr., and the residue left by evaporation was decomposed with boiling water (250 c.c.). The mixture was distilled and the distillate (150 c.c.) treated with saturated aqueous 2:4-dinitrophenylhydrazine hydrochloride. The precipitate formaldehyde 2:4-dinitrophenylhydrazone (400 mg., 30%) formed orange needles (from methanol), m. p. and mixed m. p. 168° (Found: C, 40·0; H, 2·9. Calc. for $C_7H_6O_4N_4$: C, 40·0; H, 2·9%). The residual solid, dissolved in ether, was washed with water (100 c.c.) and aqueous potassium hydroxide (3%; 3400 c.c.), a potassium salt separating at the solvent interface. The salt was collected and suspended in water (100 c.c.), the mixture acidified with 2N-sulphuric acid, and the precipitate removed in ether. The product, an *acid acetate* (520 mg.), separated from aqueous acetone as prisms, $[\alpha]_D$ +54° (*c* 0·4), m. p. 204—206° (Found: C, 75·5, 75·7; H, 10·1, 10·3. $C_{32}H_{44}O_4$ requires C, 75·6; H, 10·0. $C_{30}H_{46}O_4$ requires C, 75·9; H, 10·1%). With ethereal diazomethane it gave a *methyl ester*, needles (from methanol), m. p. 122° (Found: C, 76·3; H, 9·9; OMe, 5·8. $C_{33}H_{46}O_4$ requires C, 75·9; H, 10·1; OMe, 6·7. $C_{32}H_{44}O_4$ requires C, 76·2; H, 10·2; OMe, 6·5%). The neutral, non-volatile, ozonolysis product was fractionated by Girard-T reagent. Attempted chromatographic purification of the non-ketonic material was unsuccessful; the ketonic product (1·1 g.), by crystallisation from methanol, gave demethyloxo-*cyclo*eucalanyl acetate of m. p. 96—97° identical with that described above. In the Zimmermann reaction the ketone gave a violet colour, fading after dilution with alcohol.

The *hetoxime* separated from aqueous ethanol as needles, m. p. 170° (Found: C, 76·5;

H, 10·4; N, 2·95. $C_{22}H_{33}O_3N$ requires C, 76·9; H, 10·7; N, 2·8%), and the 2 : 4-*dinitrophenylhydrazone* from xylene–ethanol in needles, m. p. 202—203° (Found: N, 8·4. $C_{28}H_{36}O_6N_6$ requires N, 8·4%); light absorption: $\lambda_{max.}$ 368 mμ (ε 22,400).

The crude 2 : 4-dinitrophenylhydrazone from the volatile ozonolysis product of *cyclo*eucalenyl acetate was subjected to paper partition chromatography in a heptane–methanol atmosphere with heptane as the mobile phase. It was thus shown to be homogeneous, the R_F value corresponding exactly with that of formaldehyde 2 : 4-dinitrophenylhydrazone, and no trace of acetone could be detected.

(ii) *With potassium permanganate.* A mixture of *cyclo*eucalenyl acetate (5 g.) in acetone (500 c.c.), and aluminium sulphate (6 g.), was stirred while potassium permanganate (8 g.) in acetone (150 c.c.) was added during 30 min. The resulting mixture was heated under reflux for 4 hr., cooled, and filtered, and the acetone was evaporated. The residual yellow oil (4·1 g.) was fractionated by Girard-T reagent. The non-ketonic portion consisting of *cyclo*eucalenyl acetate (1·6 g.) formed needles (from chloroform–methanol), m. p. and mixed m. p. 110°. Crystallisation of the ketonic fraction from methanol gave demethyloxo*cyclo*eucalanyl acetate (1·5 g.), m. p. and mixed m. p. 96—97°. The ketone was recovered (95%) after treatment for 15 min. at 60°, in dioxan solution, with aqueous potassium iodide–iodine.

*Demethyloxo*cyclo*eucalanol.*—Hydrolysis of demethyloxo*cyclo*eucalanyl acetate (500 mg.) with 10% methanolic potassium hydroxide (25 c.c.), and repeated recrystallisation of the product from aqueous acetone gave *demethyloxo*cyclo*eucalanol* as needles, m. p. 110—111° (Found: C, 81·3; H, 11·2. $C_{20}H_{36}O_2$ requires C, 81·4; H, 11·4%). The *oxime* crystallised from aqueous ethanol in needles, m. p. 150° (Found: C, 78·4; H, 11·3; N, 3·3. $C_{20}H_{37}O_2N$ requires C, 78·7; H, 11·2; N, 3·1%), and the 2 : 4-*dinitrophenylhydrazone* as needles (from xylene–ethanol), m. p. 222—224° (Found: C, 68·9; H, 8·9; N, 9·2. $C_{34}H_{54}O_5N_4$ requires C, 69·4; H, 8·7; N, 9·0%).

*Demethylhydroxy*cyclo*eucalanyl Acetate.*—Demethyloxo*cyclo*eucalanyl acetate (1 g.) in methanol (60 c.c.) was treated with sodium borohydride (300 mg.) in methanol (5 c.c.) at room temperature for 24 hr. Crystallisation of the product from aqueous methanol afforded *demethylhydroxy*cyclo*eucalanyl acetate* as needles, $[\alpha]_D$ +60° (*c* 1·2), m. p. 123—126° (Found: C, 78·9; H, 10·9. $C_{32}H_{54}O_3$ requires C, 79·0; H, 11·2%). Acetylation with pyridine–acetic anhydride at room temperature for 24 hr. gave *demethylhydroxy*cyclo*eucalanyl diacetate*, needles (from chloroform–methanol), m. p. 138—140° (Found: C, 77·3; H, 10·2; OAc, 16·3. $C_{34}H_{56}O_5$ requires C, 77·2; H, 10·6; OAc, 16·3%).

*Dehydration of Demethylhydroxy*cyclo*eucalanyl Acetate and Ozonolysis of the Product.*—The alcohol monoacetate (500 mg.) in dry pyridine (5 c.c.) was heated with phosphorus oxychloride (1·3 c.c.) on a steam-bath for 1·5 hr. The mixture was then poured on ice (200 g.) and hydrochloric acid (6·5 c.c.), and the dehydration product (340 mg.) extracted with ether and crystallised from methanol–chloroform. It consisted of needles, $[\alpha]_D$ +54° (*c* 0·6), m. p. 96—100° (Found: C, 79·6; H, 10·5%), which gave a strong yellow colour with tetranitromethane; light absorption: $\varepsilon_{210} = 1400$, $\varepsilon_{220} = 224$, $\varepsilon_{210}/\varepsilon_{220} = 6·27$.

Ozonolysis of the dehydration product (700 mg.) in acetic acid (50 c.c.) for 40 min., followed by treatment with water (200 c.c.) and distillation into saturated aqueous 2 : 4-dinitrophenylhydrazine hydrochloride, gave acetone 2 : 4-dinitrophenylhydrazone (110 mg. 25%) as orange needles (from methanol), m. p. and mixed m. p. 125—126° (Found: C, 45·3; H, 3·8; N, 23·9. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2; N, 23·5%). The involatile product was dissolved in ether and washed with water (100 c.c.) and aqueous potassium hydroxide (3%; 3 × 100 c.c.), solid separating at the interface. This potassium salt was collected and shaken with aqueous sulphuric acid, and the product, which consisted of an *acid acetate*, collected with ether. It separated from aqueous acetone as elongated prisms (260 mg.), $[\alpha]_D$ +59° (*c* 1·1), m. p. 193—195° (Found: C, 75·6; H, 9·8%; equiv., 468. $C_{30}H_{46}O_4$ requires C, 75·9; H, 10·1%; equiv., 458). With ethereal diazomethane the acid formed a *methyl ester acetate*, needles (from aqueous methanol), m. p. 99—100° (Found: C, 75·7; H, 10·1; OMe, 5·9. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2; OMe, 6·5%).

Isomerisation of cyclo*Eucalanyl Acetate.*—(i) Hydrogen chloride was bubbled through a solution of the acetate (1 g.) in chloroform (50 c.c.) at 0° for 1·5 hr. and the mixed product (800 mg.), isolated in the usual manner, crystallised from chloroform–methanol. It formed needles, $[\alpha]_D$ +66° (*c* 0·5), m. p. 118—127° (Found: C, 81·9; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·8; H, 11·6%), exhibiting a strong yellow colour with tetranitromethane; light absorption: $\varepsilon_{210} = 3710$, $\varepsilon_{220} = 938$, $\varepsilon_{210}/\varepsilon_{220} = 3·96$.

(ii) *cyclo*Eucalanyl acetate (200 mg.) was dissolved in acetic acid (10 c.c.), and concentrated

hydrochloric acid (2 c.c.) added. The solution was then heated under reflux for ½ hr. and poured into water. Extraction with ether gave needles (130 mg.) (from chloroform–methanol), $[\alpha]_D$ +64° (*c* 0·6), m. p. 119—130°, unaffected when mixed with a sample of the acetate obtained as in (i).

Eucalenyl Acetate.—(i) Numerous crystallisations of the mixture, m. p. 118—127° (800 mg.), from chloroform–methanol gave *eucalenyl acetate* (50 mg.) as needles, $[\alpha]_D$ +85° (*c* 0·6), m. p. 120—122° (Found: C, 81·7; H, 11·5. $C_{32}H_{50}O_2$ requires C, 81·8; H, 11·6%); light absorption: $\varepsilon_{210} = 3400$, $\varepsilon_{220} = 277$, $\varepsilon_{210}/\varepsilon_{220} = 12·4$.

(ii) Chromic oxide (660 mg.) in 90% acetic acid (30 c.c.) was added during 5 min. to a solution of the mixed acetates (1·6 g.) in acetic acid (100 c.c.) at 93°. After further heating for 10 min., the liquid was diluted with water, and the precipitate (1·65 g.) isolated with ether. A solution of the product in light petroleum (100 c.c.) was filtered through a column (2·1 × 18 cm.) of alumina (60 g.) which was then eluted with (*a*) light petroleum (1 l.), (*b*) light petroleum–benzene (9 : 1; 500 c.c.), (*c*) light petroleum–benzene (4 : 1; 500 c.c.), (*d*) benzene (350 c.c.), and (*e*) benzene–ether (1 : 1; 1 l.). The combined fractions (*a*) and (*b*) were evaporated, and the product (450 mg.) twice crystallised from chloroform–methanol to give eucalenyl acetate, m. p. and mixed m. p. 120—122°.

Dioxoeucalenyl Acetate.—Fraction (*d*) from the above chromatogram yielded a yellow crystalline solid (460 mg.), which crystallised from methanol to give *dioxoeucalenyl acetate* as light yellow blades, $[\alpha]_D$ +98° (*c* 1·3), m. p. 157° (Found: C, 77·0; H, 9·9. $C_{32}H_{48}O_4$ requires C, 77·3; H, 10·2%); light absorption: $\lambda_{max.}$ 271 mμ (ε 7600). Hydrolysis of dioxoeucalenyl acetate with 5% methanolic potassium hydroxide gave *dioxoeucalenol*, as pale yellow needles (from methanol), m. p. 165° (Found: C, 78·9; H, 10·3. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%); light absorption: $\lambda_{max.}$ 271 mμ (ε 6300), 344 mμ (ε 96).

Oxoeucalenyl Acetate.—(i) Chromic oxide (250 mg.) in acetic acid (50 c.c.) was added during 1 hr. to a boiling solution of eucalenyl acetate (450 mg.) in acetic acid (50 c.c.) and the heating continued for 2 hr. The neutral product, isolated with ether, was dissolved in light petroleum (25 c.c.), and the solution filtered through a column (5·0 × 2·2 cm.) of alumina (20 g.). Elution with light petroleum (500 c.c.) and light petroleum–benzene (4 : 1; 500 c.c.) gave a fraction consisting of eucalenyl acetate (100 mg.) which separated from chloroform–methanol as needles, m. p. and mixed m. p. 120—122°. Elution of the chromatogram with benzene (500 c.c.) and benzene–ether (9 : 1; 500 c.c.) gave a solid (270 mg.) which, after several crystallisations from methanol, yielded *oxoeucalenyl acetate* as blades, $[\alpha]_D$ +76° (*c* 0·3), m. p. 136° (Found: C, 79·2; H, 10·9. $C_{32}H_{54}O_3$ requires C, 79·5; H, 10·9%); light absorption: $\lambda_{max.}$ 241 mμ (ε 3400), not giving a colour with tetranitromethane.

(ii) Fraction (*e*) from the chromatogram used in the separation of eucalenyl acetate consisted of oxoeucalenyl acetate (100 mg.) which when recrystallised from methanol gave blades, m. p. and mixed m. p. 136°.

Dioxoeucalanyl Acetate.—Zinc dust (1·2 g.) was slowly added to a boiling solution of dioxoeucalenyl acetate (300 mg.) in acetic acid (15 c.c.) and the heating continued for 1 hr. *Dioxoeucalanyl acetate*, isolated by means of ether, crystallised from methanol in plates, m. p. 198—200° (Found: C, 77·3; H, 10·6. $C_{32}H_{54}O_4$ requires C, 77·0; H, 10·6%); light absorption: $\lambda_{max.}$ 290 mμ (ε 67).

Eucalanyl Acetate.—A solution of the isomerised acetates, m. p. 118—127° (1 g.), from *cyclo*eucalanyl acetate, in acetic acid (100 c.c.), was shaken with hydrogen and platinum (650 mg.) at 80° for 24 hr. The product crystallised from chloroform–methanol in needles, m. p. 115—120°. The hydrogenation caused a significant drop in the light-absorption intensity in the ethylenic region from λ = 1920 to λ = 2140. Light absorption change: $\varepsilon_{210} = 3680$, $\varepsilon_{220} = 910$, $\varepsilon_{210}/\varepsilon_{220} = 4·05$ before hydrogenation; $\varepsilon_{210} = 1600$, $\varepsilon_{220} = 457$, $\varepsilon_{210}/\varepsilon_{220} = 3·48$ after hydrogenation. A solution of the reduced material in acetic acid (100 c.c.) was treated on a steam-bath with chromic oxide (850 mg.) in acetic acid (45 c.c.) added during 30 min. After further heating, the mixture was set aside overnight, the neutral product (1·0 g.) being then isolated with ether. When dissolved in light petroleum (100 c.c.) it was chromatographed on alumina (30 g.), elution with light petroleum (500 c.c.) giving *eucalanyl acetate* (300 mg.) which crystallised from chloroform–methanol as needles, $[\alpha]_D$ +56° (*c* 0·8), m. p. 132° (Found: C, 81·4; H, 11·7. $C_{32}H_{56}O_2$ requires C, 81·4; H, 12·0%). Elution with light petroleum–benzene (4 : 1; 500 c.c.) and benzene (500 c.c.) yielded a fraction (90 mg.) separating from methanol as pale yellow needles, m. p. 155—157°, alone or mixed with dioxoeucalenyl acetate.

Eucalanol.—Hydrolysis of eucalanyl acetate in 5% ethanolic potassium hydroxide gave *eucalanol* which crystallised from chloroform–methanol in needles, m. p. 167—169° (Found:

C, 83·4; H, 12·8. $C_{31}H_{56}O$ requires C, 83·7; H, 12·7%), which remained colourless in tetranitromethane.

Epoxyeucalanyl Acetate.—A mixture of eucalenyl acetate (200 mg.) and perhydrol (1 c.c.) in acetic acid (100 c.c.), heated on the steam-bath for 2 hr. and then diluted with water, gave *epoxyeucalanyl acetate* (100 mg.) which crystallised from chloroform–methanol as plates, m. p. 141—143° (Found: C, 79·3; H, 10·9. $C_{32}H_{56}O_3$ requires C, 79·1; H, 11·3%). The compound gave a negative tetranitromethane reaction and had no selective ultraviolet light absorption.

Demethylcycloeucalanol.—The ketone acetate (430 mg.) in anhydrous hydrazine (5 c.c.) and absolute alcohol (20 c.c.) containing dissolved sodium (620 mg.) was heated at 180° for 18 hr. The cooled mixture was diluted with water and extracted with ether. The product (370 mg.) crystallised from aqueous methanol, affording *demethylcycloeucalanol* as needles, $[\alpha]_D$ +33° (*c* 0·4), m. p. 126—127° (Found: C, 84·1; H, 12·3. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). Acetic anhydride–pyridine at room temperature (24 hr.) gave *demethylcycloeucalanyl acetate* as needles (from chloroform–methanol), $[\alpha]_D$ +57° (*c* 1·0), m. p. 98—100° (Found: C, 81·9; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%).

Rearrangement of Demethylcycloeucalanyl Acetate with Hydrogen Chloride.—Demethylcycloeucalanyl acetate (350 mg.) in dry chloroform (30 c.c.) was isomerised as for the higher homologue with hydrogen chloride at 0°. After 45 min., the *product* was isolated in the usual manner and crystallised from chloroform–methanol as plates (300 mg.), m. p. 108—112° (Found: C, 81·9; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%); light absorption: $\varepsilon_{310} = 3940$, $\varepsilon_{320} = 777$, $\varepsilon_{310}/\varepsilon_{320} = 5{\cdot}08$.

Demethyleucalenyl Acetate.—Chromic oxide (500 mg.) in 90% acetic acid (20 c.c.) was added during 5 min. to a solution of the mixed acetates of m. p. 108—112° (950 mg.) in acetic acid (80 c.c.) at 93°. Further heating for 10 min. and then treatment with water led to a product (960 mg.), which was isolated with ether, dissolved in light petroleum (80 c.c.), chromatographed on alumina (30 g.), and eluted with (*a*) light petroleum (300 c.c.), (*b*) light petroleum–benzene (9 : 1; 300 c.c.), (*c*) light petroleum–benzene (4 : 1; 600 c.c.), (*d*) benzene (300 c.c.), and (*e*) ether (500 c.c.). The combined contents (150 mg.) of fractions (*b*) and (*c*), twice crystallised from methanol, yielded *demethyleucalenyl acetate* as needles, m. p. 110—111° (Found: C, 81·5; H, 11·6. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%).

Demethyldioxoeucalenyl Acetate.—Evaporation of fraction (*d*) from the above chromatogram left a residue (170 mg.) which, when crystallised from methanol, gave *demethyldioxoeucalenyl acetate* as pale yellow blades, m. p. 151—153° (Found: C, 76·7; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·1; H, 10·1%); light absorption: $\lambda_{max.}$ 271 mμ (ε 7200).

Demethyloxoeucalenyl Acetate.—Evaporation of fraction (*e*) afforded a solid (100 mg.) consisting of *demethyloxoeucalenyl acetate* and crystallising from methanol in plates, m. p. 141° (Found: C, 78·9; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%); light absorption: $\lambda_{max.}$ 241 mμ (ε 10,200).

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282. *Conductivity Studies of Some Thiosulphates in Aqueous Methanol and in Aqueous Ethanol.*

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The conductivities of sodium, potassium, magnesium, calcium, and strontium thiosulphates have been measured in 44% aqueous ethanol,* and the sodium salt in 20%, 50%, and 80% aqueous methanol. The dissociation constants of the ion-pairs have been calculated.

IN order to consider the effect of incomplete dissociation of some thiosulphates in reaction rates involving these salts, their dissociation constants have been obtained by Davies's conductivity methods.[1] The conductivity measurements and the resultant calculations

* In this and the following two papers, *e.g.*, 44% aqueous alcohol denotes 44 parts by wt. of alcohol contained in 100 parts of solution.

[1] Davies, *Trans. Faraday Soc.*, 1927, **23**, 351.

are given in Tables 1, 2, and 3, where c = equivs./l., Λ = equivalent conductivity, K = dissociation constant of the ion-pairs, and b, b_1, and b_2 are the Onsager factors referred to later.

TABLE 1. *Conductivity of sodium thiosulphate in aqueous methanol at 25°.*

20% (w/w) Methanol; $\Lambda_0 = 92{\cdot}56$; $b_1 = 111{\cdot}3$; $b_2 = 58{\cdot}6$.							
10^4c	4·2116	5·0219	6·3985	6·6299	9·2036	10·972	14·121
Λ	89·60	89·31	88·88	88·79	88·10	87·61	86·89
K	0·12	0·12	0·12	0·11	0·12	0·11	0·10
50% (w/w) Methanol; $\Lambda_0 = 72{\cdot}65$; $b_1 = 118{\cdot}1$; $b_2 = 60{\cdot}9$.							
10^4c	3·0415	4·1464	5·0964	6·4248	7·8016	10·299	16·184
Λ	69·68	69·13	68·70	68·12	67·63	66·79	65·14
10^3K	2·52	2·62	2·48	2·47	2·54	2·54	2·52
80% (w/w) Methanol; $\Lambda_0 = 81{\cdot}20$; $b_1 = 206{\cdot}9$; $b_2 = 107{\cdot}4$.							
10^4c	3·0159	3·9043	4·7769	5·4463	6·4692	7·8324	9·5171
Λ	74·41	73·32	72·68	71·68	70·72	69·56	68·32
10^3K	4·40	4·44	4·47	4·48	4·47	4·48	4·52

TABLE 2. *Conductivity of potassium thiosulphate in 20% (w/w) methanol at 25°.*

			$\Lambda_0 = 106{\cdot}96$; $b_1 = 116{\cdot}5$; $b_2 = 62{\cdot}5$.				
10^4c	2·9152	3·7230	4·6076	5·2215	6·1791	7·4172	10·942
Λ	104·29	103·91	103·53	103·26	102·92	102·54	101·45
10^3K	6·8	6·9	6·8	6·2	6·5	7·1	6·8

TABLE 3. *Conductivities of magnesium, calcium, strontium, sodium, and potassium thiosulphates in 44·05% (w/w) ethanol.*

Magnesium: 20°; $\Lambda_0 = 43{\cdot}05$; $b = 116{\cdot}5$.							
10^4c	2·7791	3·5083	4·9022	6·9794	9·2837	9·8065	
Λ	34·67	33·59	32·01	29·94	28·25	27·97	
10^4K	4·95	4·96	4·95	4·95	4·93	4·94	
Magnesium: 25°; $\Lambda_0 = 50{\cdot}55$; $b = 139{\cdot}4$.							
10^4c	2·3981	2·6037	3·0742	3·6590	3·7591	6·0142	7·6791
Λ	41·24	40·86	39·88	38·92	38·73	35·76	34·08
10^4K	4·68	4·72	4·67	4·70	4·68	4·70	4·63
Magnesium: 30°; $\Lambda_0 = 59{\cdot}24$; $b = 166{\cdot}7$.							
10^4c	2·4998	3·4686	3·6801	5·3954	7·0260	7·6633	9·9301
Λ	47·75	45·41	45·17	42·12	40·23	39·33	37·41
10^4K	4·43	4·35	4·38	4·40	4·41	4·38	4·39
Calcium: 25°; $\Lambda_0 = 52{\cdot}25$; $b = 142{\cdot}3$.							
10^4c	1·8578	2·5581	3·0154	3·6191	4·0461	4·9162	6·0350
Λ	42·20	40·24	39·20	37·90	37·15	35·82	34·18
10^4K	3·26	3·25	3·26	3·23	3·25	3·26	3·20
Strontium: 25°; $\Lambda_0 = 52{\cdot}15$; $b = 142{\cdot}1$.							
10^4c	1·9432	2·1851	2·5653	3·0052	3·0830	4·1010	5·2311
Λ	40·51	39·77	38·68	37·62	37·39	35·39	33·55
10^4K	2·60	2·61	2·60	2·61	2·59	2·61	2·60
Sodium: 25°; $\Lambda_0 = 51{\cdot}30$; $b_1 = 82{\cdot}6$; $b_2 = 42{\cdot}6$.							
10^4c	2·6246	3·5295	4·2758	6·8994	7·9731	9·6160	
Λ	49·20	48·78	48·52	47·60	47·25	46·80	
10^3K	1·47	1·43	1·49	1·46	1·42	1·42	
Potassium: 25°; $\Lambda_0 = 57{\cdot}50$; $b_1 = 86{\cdot}0$; $b_2 = 45{\cdot}1$.							
10^4c	2·3407	2·8582	4·1840	4·9764	5·0228	6·0654	
Λ	55·31	55·05	54·39	54·05	53·98	53·62	
10^3K	1·18	1·21	1·16	1·15	1·14	1·16	

Approximate values of Λ_0 were obtained by extrapolation of the plots of Λ against $\sqrt{c}$. For the sodium and potassium salts, except in 80% methanol, more precise values of Λ_0 were then found by Onsager's method,[2] *i.e.*, by plotting $(\Lambda + b\sqrt{c})$ against c, where b is

[2] Onsager, *Phys. Z.*, 1927, **28**, 277.

the calculated coefficient of Onsager's conductivity expression, $\Lambda = \Lambda_0 - bI^{\frac{1}{2}}$, I being the ionic strength. For these extrapolations it was assumed that $I = c$. The physical constants used were taken from recent data,[3] and the dielectric constants [4] D, the viscosities [5] η, and the densities [6] d used in working out the results are :

Solvent	Temp.	D	$10^3\eta$	d	Solvent	Temp.	D	$10^3\eta$	d
20% Methanol	25°	69·2	13·90	0·9641	44·05% Ethanol	20°	53·95	28·71	0·9267
50% Methanol	25	54·8	15·42	0·9134	,,	25	52·50	23·85	0·9229
80% Methanol	25	40·7	10·12	0·8433	,,	30	51·12	20·06	0·9189

For the other examples the methods of Davies [1] and of Owen [7] were used in obtaining Λ_0.

The dissociation constants of the alkaline-earth thiosulphates were derived by first inserting Λ_0 for Λ_x on the right-hand side of

$$\Lambda_x = \Lambda_0 - b(\Lambda_c/\Lambda_x)^{\frac{1}{2}}$$

where Λ_x represents the conductivity at an ionic concentration of $\alpha c = \Lambda c/\Lambda_x$ and where α is the degree of dissociation. Values of Λ_x were successively tried in the equation until constant figures were reached. The dissociation constants were then calculated from :

$$K = \alpha^2 c f_M f_{S_2O_3}^2/(1 - \alpha)$$

for which the mean ion activity coefficients were obtained from the limiting form of the Debye–Hückel expression :

$$-\log f_i = 1{\cdot}8246 \times 10^6 z_i^2 (DT)^{-\frac{3}{2}} I^{\frac{1}{2}}$$

Here z_i is the ion valency, and the ionic strength $I = 2\alpha c$.

The sodium and potassium data were treated similarly. We have

$$\Lambda = (\beta/2)(\Lambda_{0,1} - b_1 I^{\frac{1}{2}}) + (1 - \beta)(\Lambda_{0,2} - b_2 I^{\frac{1}{2}})$$

where $\Lambda_{0,1}$ is the sum of the mobilities of the M^+ and the $MS_2O_3^-$ species, $\Lambda_{0,2}$ is the sum of the M^+ and $S_2O_3^{2-}$ mobilities, and b_1 and b_2 are the respective Onsager factors. The fraction of salt present as ion-pairs is represented by β and $I = c(1{\cdot}5 - \beta)$. The mobility of the $MS_2O_3^-$ ion-pair is rather uncertain and we have estimated it as follows. In water the mobility [8] of the thiosulphate ion is 87·4; and from the figures for the alkaline-earth cations in water [9] and the values of Λ_0 for their thiosulphates in 44% ethanol the ratio Λ_0 (44% ethanol)/Λ_0 (water) = 0·36. We have therefore taken Λ_0 for the thiosulphate ion to be $87{\cdot}4 \times 0{\cdot}36 = 31{\cdot}3$ and thus assumed $NaS_2O_3^-$ and $KS_2O_3^-$ to have the value of 16·0. Calculation shows that an error of 1 unit has little effect on the value of K. By similar comparisons we deduce 29·0 for the $NaS_2O_3^-$ ion-pair in 20% methanol, 23·0 in 50% methanol, and 26·0 in 80% methanol. The average dissociation constants are given in Table 4.

Among the numerous factors which influence the extent to which ions associate in solution is their effective size. Where essentially electrostatic interaction occurs, Bjerrum[10] has proposed a quantitative relation between the dissociation constant and the effective radius of the ion pair. These values (a in Å) are given in Table 4, together with the corresponding figures for water as solvent. Except for $KS_2O_3^-$ in 44% ethanol, the effective radii of the ion-pairs in water are bigger, implying that in mixed solvents ion-hydration tends to decrease.

[3] Rossini, Gucker, Johnston, and Pauling, and Vinal, *J. Amer. Chem. Soc.*, 1952, **74**, 2699.
[4] Akerlöf, *ibid.*, 1932, **54**, 4125; Broach and Amis, *J. Chem. Phys.*, 1954, **22**, 39.
[5] (*a*) "International Critical Tables," Vol. V, p. 22; (*b*) Tammann and Pillsburg., *Z. anorg. Chem.*, 1928, **172**, 250.
[6] Ref. 5*a*, Vol. III, pp. 111—116.
[7] Owen, *J. Amer. Chem. Soc.*, 1939, **61**, 1393.
[8] Denney and Monk, *Trans. Faraday Soc.*, 1951, **47**, 992.
[9] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1950, p. 172.
[10] Bjerrum, *Kgl. danske Videnshab. Selskab, Mat.-fys. Medd.*, 1926, **7**, No. 9.

TABLE 4. *Collected data.*

Ion-pair	Solvent	10^4K (solvent)	10^4K (water)	a (solvent)	a (water)	R
$NaS_2O_3^-$	44% EtOH	144	2100	3·84	5·5	0·999
$KS_2O_3^-$	44% EtOH	117	1200	3·41	3·9	0·957
MgS_2O_3	44% EtOH	4·67	145	4·47	8·5	0·963
CaS_2O_3	44% EtOH	3·25	104	4·15	7·1	0·952
SrS_2O_3	44% EtOH	2·60	92	4·00	6·4	0·951
MgS_2O_3 (20°) ...	44% EtOH	4·95	—	—	—	—
MgS_2O_3 (30°) ...	44% EtOH	4·39	—	—	—	—
$KS_2O_3^-$	44% EtOH	680	1200	4·46	3·9	1·029
$NaS_2O_3^-$	20% MeOH	1100	2100	5·32	5·5	1·042
$NaS_2O_3^-$	50% MeOH	243	2100	4·69	5·5	0·913
$NaS_2O_3^-$	80% MeOH	45	2100	4·07	5·5	0·669

A semiquantitative relation between ion mobilities and their radii is expressed by Stokes's law, which in terms of limiting mobilities becomes

$$r_i = 8{\cdot}197 \times 10^{-9}\, z_i/\lambda_0\eta$$

where r_i is the ion radius, z_i is its valency, and λ_0 is its limiting mobility. In terms of anion and cation this may be written

$$\eta(\lambda_{0,1} + \lambda_{0,2}) = \eta\Lambda_0 = 8{\cdot}197 \times 10^{-9}(z_1/r_1 + z_2/r_2)$$

When the radii remain constant we have the familiar Walden's rule,[11] $\Lambda_0\eta$ = constant, whence, $\Lambda_0\eta$ (water) = $\Lambda_0\eta$ (solvent). The ratio of these two is given in Table 4 under R. Except for 50% and 80% methanol these are all within 5% of unity implying that no real change takes place in the effective radii of the ions until the alcohol content becomes high. This is in contrast to the deductions made above on the basis of Bjerrum's treatment, and seems to imply that in solvents of lower dielectric constant where the dissociation constants become much smaller the forces of ion-association are no longer purely electrostatic.

When the conventional thermodynamic functions are applied to the data for magnesium thiosulphate in 44% ethanol the following figures emerge where ΔH° is the heat of dissociation and ΔS° is the corresponding entropy change:

$$\Delta H^\circ\,(20\text{—}25^\circ) = -2{\cdot}16,\ \Delta H^\circ\,(25\text{—}30^\circ) = -2{\cdot}10\ \text{kcal./mole};\ \Delta S^\circ\,(25^\circ) = -22{\cdot}0$$

The ΔS° value is very close to that found for several thiosulphates in aqueous solution.[12]

EXPERIMENTAL

The conductivity apparatus has been described elsewhere.[13] The conductivity water was prepared by a mixed ion-exchange resin column.[14] Pure ethanol and methanol were prepared by shaking the commercial alcohols with quicklime, allowing the whole to stand several days, and then distilling under nitrogen. The solvents were made up by weight and stored under nitrogen.

" AnalaR " sodium thiosulphate was recrystallised from water below 80° and dried at 35°. The equivalent weight was found for each batch by titration against standard potassium iodate. Potassium thiosulphate of B.D.H. Laboratory Reagent grade was recrystallised four times. Magnesium thiosulphate was made by adding magnesium sulphate solution dropwise to a stirred suspension of barium thiosulphate in slight excess. After filtration the solution was evaporated under a vacuum at 35° till crystals were formed. The solution was filtered and most of the remaining barium thiosulphate precipitated by alcohol. The magnesium salt crystallised from the filtrate after evaporation at 25°, and was recrystallised 3 times from alcohol–water. Determinations of equivalent weight showed the crystals to be $MgS_2O_3.6H_2O$. Strontium thiosulphate crystallised when concentrated sodium thiosulphate and strontium chloride

[11] Walden, *Z. phys. Chem.*, 1912, **78**, 257.
[12] Gimblett and Monk, *Trans. Faraday Soc.*, 1955, **51**, 793.
[13] Davies, *J.*, 1937, 432; Davies and Monk, *J.*, 1949, 413.
[14] Davies and Nancollas, *Chem. and Ind.*, 1950, 129.

solutions were dripped into a small volume of ice-water; the crystals were washed with aqueous ethanol and recrystallised three times from water; they proved to be $SrS_2O_3,5H_2O$. Alcohol was added to a saturated solution of B.D.H. calcium thiosulphate until about 10% had been precipitated; this was filtered off and discarded; most of the remainder was precipitated by alcohol, then redissolved, and the procedure was repeated thrice; the crystals obtained were $CaS_2O_3,5H_2O$.

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283. *The Influence of Electrolytic Dissociation upon Rates of Reactions. Part II.* The Thiosulphate–Propyl Bromide Reaction in Aqueous Ethanol.*

By J. R. BEVAN and C. B. MONK.

The rate of reaction between various thiosulphates and *n*-propyl bromide in 44% ethanol has been followed. It being assumed that the ion-pairs present in solution do not contribute to the reaction velocity, the velocity constants for the reaction with the free thiosulphate ion are found to be independent of the cations present and of the ionic strengths of the solutions. The constants obtained are considerably higher than those based upon stoicheiometric thiosulphate molarities, but over a temperature range the results lead to the same value for the energy of activation. The *iso*propyl bromide reaction is also briefly discussed.

THE reaction $S_2O_3^{2-} + RBr \rightleftharpoons RS_2O_3^- + Br^-$, where R is an alkyl group, is, according to Crowell and Hammett,[1] bimolecular, irreversible, and relatively fast. The resulting alkyl Bunte salt is reasonably stable but, since hydrolysis of the alkyl bromide can render the solutions acidic, buffers such as acetates must be present to prevent decomposition of the thiosulphate ion.

Now in the solvent used by Crowell and Hammett,[1] namely, 44% (w/w) ethanol, the sodium thiosulphate used, from the evidence supplied in the preceding paper, is incompletely dissociated. We have endeavoured to see what is the effect of this by assuming that the essential reaction is between alkyl bromide and free thiosulphate ion. We have examined this feature in detail, using not only sodium but also other thiosulphates. Where bivalent cations M^{2+} were used, the presence of $MRS_2O_3^+$ and MAc^+ also had to be considered. This information was obtained from some solubility studies described below.

Kinetic Measurements.—A typical run in which calcium thiosulphate was used is shown in Table 1. The penultimate column records the velocity constants (k) (mole $l.^{-1}$ $sec.^{-1}$),

TABLE 1. *Reaction of calcium thiosulphate with* n-*propyl bromide in* 44% (*w/w*) *ethanol at* 25°.

Initial concns.: CaS_2O_3 = 0·05250M; Pr^nBr = 0·04431M; NaOAc = 0·0050M.

t (min.)	$10^3[Pr^nS_2O_3^-]$	$10^4[CaOAc^+]$	$10^4[CaPr^nS_2O_3^+]$	$10^4[NaS_2O_3^-]$	10^4k	$10^4k/\alpha$
65	2·77	8·9	4·8	8·4	3·83	10·46
115	4·53	9·1	8·9	8·0	3·80	10·50
206	7·93	9·3	14·8	7·3	3·68	10·42
277	9·14	10·0	18·5	6·8	3·64	10·43

calculated on the assumption that ion-pairing is absent. The concentrations of $NaS_2O_3^-$ were calculated from the known dissociation constant (see preceding paper), and those of $CaOAc^+$ and $CaPr^nS_2O_3^+$ from the solubility results reported below. In the final column the ratio k/α represents the velocity constant for the reaction between alkyl bromide and free thiosulphate ion, α being the fraction of total thiosulphate present as $S_2O_3^{2-}$. This

* Part I, *J.*, 1955, 1899.

[1] Crowell and Hammett, *J. Amer. Chem. Soc.*, 1948, **70**, 3444.

was obtained by using the dissociation constant of CaS_2O_3 established by conductivity measurements in the preceding paper. The concentrations of ion-pairs were calculated from the general expression :

$$\log [\text{ion-pair}] = \log [\text{cation}][\text{anion}] - \log K - nf(I)$$

and a form of Davies's activity coefficient expression, *i.e.* :

$$-\log f_i = z_i^2 \times 0{\cdot}932\{I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0{\cdot}2I\} = f(I)$$

In these, z_i = ion valency, I = ionic strength, and $n = z^2(\text{anion}) + z^2(\text{cation}) - z^2$ (ion-pair).

A series of approximations was needed to establish the true concentrations. A number of runs were analysed in this fashion and are summarised in Table 2. In the runs at the higher concentrations of thiosulphate, k changed slowly with time (see Table 1); the values given in Table 2 are those obtained by extrapolation to $t = 0$.

TABLE 2. *Reaction of thiosulphates with* n-*propyl bromide in* 44·05% (*w*/*w*) *ethanol at* 25°.

Salt	10^4[thiosulphate]	10^4[Pr^{n}Br]	10^4[NaOAc]	10^4k	$10^4k/\alpha$
$Na_2S_2O_3$	7·943	4·217	1·25	9·44	10·15
	15·62	8·431	2·5	9·05	10·3
	37·51	19·23	5·0	8·29	10·2
	59·76	24·76	6·1	7·73	10·15
	207·3	111·0	8·4	6·54	10·15
	526·2	443·1	50·0	5·73	10·3
$K_2S_2O_3$	10·26	5·164	1·0	9·12	10·15
	50·13	25·36	4·0	7·52	10·3
	528·1	443·1	50·0	5·13	10·2
MgS_2O_3	6·984	3·423	0·20	6·88	10·3
	10·37	221·5	50·0	4·50	10·0
CaS_2O_3	525·0	443·1	50·0	3·88	10·45
SrS_2O_3	6·023	2·987	0·20	5·92	10·2
	10·47	5·036	0·50	5·35	10·3

Some runs at different temperatures have been similarly interpreted for 0·05M-magnesium thiosulphate. The figures for these are given in Table 3.

TABLE 3. *Reaction of magnesium thiosulphate and* n-*propyl bromide in* 44·05% (*w*/*w*) *ethanol at various temperatures.*

Temp.	15·0°	20·0°	25·0°	30·0°	34·5°
10^4k	1·57	2·64	4·50	7·39	11·14
$10^4k/\alpha$	3·35	5·64	9·62	15·90	24·11

Crowell and Hammett [1] also studied the reaction between the thiosulphate ion and *iso*propyl bromide in 44% ethanol. They used sodium thiosulphate and varying concentrations of sodium acetate in order to vary the ionic strength and thereby study any ion-dipole effects. We have recalculated their data, making allowance for the presence of $NaS_2O_3^-$ ion-pairs, as shown in Table 4.

TABLE 4. *Reaction of sodium thiosulphate and* iso*propyl bromide in* 44·05% *ethanol at* 25°.

$[Na_2S_2O_3]$	[Pr^{i}Br]	[NaOAc]	10^4k	$10^4k/\alpha$	I
0·10	0·05	0·02	0·294	0·62	0·215
0·10	0·10	0·10	0·25	0·59	0·285
0·15	0·10	0·10	0·22	0·57	0·366
0·20	0·10	0·10	0·18	0·50	0·444

Solubility Measurements.—In order to obtain information about the extent to which the ion-pairs $MOAc^+$, MBr^+, and $MRS_2O_3^+$ were possible members of the solutions in the kinetic studies, the solubility at 25° of calcium iodate in 44% ethanol solutions of the

[1] Davies, *J.*, 1938, 2093.

sodium salts of these substances was measured. Davies [3] has shown how the dissociation constants of calcium salts can thereby be calculated. The solubility data and consequent calculations are given in Table 5.

Our method of calculation is as follows. Let

$$S = [Ca^{2+}][IO_3^-]^2 f_{Ca} f_{IO_3}^2$$

where S is the activity solubility product. The form of Davies's activity coefficient expression referred to above was used. The calculation of S required a knowledge of the dissociation constant of the ion-pair $CaIO_3^+$. In water this [4] is 0·13. We have estimated it to be 0·009 here by multiplying the water value by the ratio of the values of $NaS_2O_3^-$ in the two solvents [5, 6] *i.e.*, by 0·0144/0·20. Our reason for doing this is that the ion-pairs are of similar valency types and have about the same dissociation constants in water. The value of S, derived by approximations, is thus $7{\cdot}93 \times 10^{-11}$ g.-ion^3 l.$^{-3}$.

In the presence of the sodium salts, $NaIO_3$ ion-pairs are also present. The dissociation

TABLE 5. *Solubility of calcium iodate in sodium acetate, sodium bromide, and sodium n-propyl thiosulphate solutions (44·0% w/w ethanol; at 25°).* (Concns.: 10^{-4} mole l.$^{-1}$.)

[NaBr]	$[Ca(IO_3)_2]$	[Salt]	$[CaIO_3^+]$	$[CaX^+]$	$[NaIO_3]$	K (CaX^+)
			X$^-$ = Acetate			
—	3·100	—	0·172	—	—	—
—	5·172	174·0	0·144	1·60	0·264	0·014
—	5·805	261·1	0·142	1·86	0·408	0·016
—	6·810	435·1	0·141	2·51	0·681	0·017
			X$^-$ = Bromide			
—	4·446	139·2	0·155	—	0·196	—
—	5·151	278·3	0·165	—	0·371	—
			X$^-$ = $Pr^nS_2O_3^-$			
462·1	8·194	442·0	0·150	2·28	1·33	0·017
647·1	9·271	617·4	0·151	2·70	1·87	0·019
924·0	10·53	882·1	0·150	3·19	2·64	0·020

constant [7] of this species in water is 3·0 and our estimate based on the figures for silver acetate in the two solvents is that K ($NaIO_3$) in 44% ethanol is about 0·4.

The expressions used are:

$$\log [Ca^{2+}] = -10{\cdot}1007 - 2 \log [IO_3^-) + 6 \times 0{\cdot}932f(I)$$

$$\log [CaIO_3^+] = \log [Ca^{2+}][IO_3^-] + 2{\cdot}046 - 4 \times 0{\cdot}932f(I)$$

$$\log [NaIO_3] = \log [Na^+][IO_3^-] + 0{\cdot}398 - 3 \times 0{\cdot}932f(I)$$

The differences between the measured solubilities and the calculated values of ($[Ca^{2+}] + [CaIO_3^+]$) represent the concentrations of CaX^+ present.

Discussion.—It is clear from Table 2 that, by assuming that the rate of reaction depends on the concentration of free thiosulphate ion, values of the velocity constant are obtained which are quite different from those based on the total thiosulphate molarity. This is particularly true at higher ionic strengths. Our average value of $k/\alpha = 10{\cdot}0 \pm 0{\cdot}2 \times 10^{-4}$ mole l.$^{-1}$ sec.$^{-1}$ at 25° is much higher than Crowell and Hammett's value of $k = 4{\cdot}74 \times 10^{-4}$. In addition, the constancy of k/α for both 2 : 1- and 2 : 2-valent salts and over a range of ionic strengths rules out any significant contribution by the charged ion-pairs $NaS_2O_3^-$ and $KS_2O_3^-$ and also indicates that ion-dipole salt effects are virtually absent.

The activation energy (E) for this reaction was calculated by Crowell and Hammett

[3] Davies, *J.*, 1938, 277.
[4] Wise and Davies, *J.*, 1938, 273.
[5] Preceding paper.
[6] Denney and Monk, *Trans. Faraday Soc.*, 1951, **47**, 992.
[7] MacDougall and Davies, *J.*, 1935, 1416.

to be 18·0 kcal. mole^{-1}. Our magnesium figures in Table 3 give a linear plot when log k/α is plotted against $1/T$, whence from the Arrhenius equation,

$$\log k/\alpha = \log A - E_A/2{\cdot}303RT$$

$E_A = 18{\cdot}1 \pm 0{\cdot}1$ kcal. mole^{-1} and $A = 1{\cdot}5 \times 10^{10}$. If k is used instead of k/α, $A = 7{\cdot}2 \times 10^{9}$. The former value of A is much the nearer general average[9] of $2{\cdot}7 \times 10^{11}$ that is found for a large number of bimolecular reactions.

Our method of calculation also gives higher figures for the reaction between *iso*propyl bromide and thiosulphate (Table 4). There is some change with ionic strength which may be due to uncertainties in the calculations or it may be due to an ion-dipole salt effect. The extrapolation of log (k/α) against I gives $7{\cdot}2 \times 10^{-5}$ mole l.$^{-1}$ sec.$^{-1}$ for the reaction rate whereas the original workers obtained $2{\cdot}94 \times 10^{-5}$.

Experimental

The preparation of the thiosulphates has been described in the preceding paper. Vogel's method[10] of preparation was used for *n*-propyl bromide. Gravimetric analysis gave 64·92% of bromine (theor., 64·96%). The sample was stored in a dark bottle and refractionated at intervals of not greater than two weeks. The iodine-titration solution was standardised against sodium thiosulphate which itself was standardised against potassium iodate.

For a run, a sample of *n*-propyl bromide was weighed into a graduated flask containing solvent. The volume was made up and the solution siphoned into a burette. A known volume was run into the graduated reaction flask, the desired amount of sodium acetate stock solution added, and the reaction flask placed in the thermostat. A stock solution of thiosulphate was made up by weight after its equivalent weight had been found by titration as described in the preceding paper. The stock solution was placed in a thermostat and the reaction was started by pipetting a portion into the reaction flask. The time of half-delivery was taken as zero. The solution in the reaction flask was made up to the mark, not more than 5 ml. of solvent being required. The whole was well shaken and a volume withdrawn by a lagged pipette stored in the thermostat. The reaction was stopped by running the contents into 100 g. of crushed ice. The time of half-delivery, usually zero plus 1 min., was taken as the time of removal. The titre at zero time was obtained by extrapolating succeeding titres against time. The weighing out of the *n*-propyl bromide was checked by hydrolysing samples with sodium hydroxide in sealed tubes at 100° and analysing the products for bromide. The values agreed with those calculated within 0·04%. In a few cases when sodium thiosulphate was used the reaction was taken to completion; the thiosulphate used was equivalent to 99·5% of the *n*-propyl bromide taken.

For very dilute solutions the end-point with starch was not good. There was a marked end-point error and this was decreased by using 10 ml. of 0·1M-potassium iodide, 5 ml. of 1% starch solution, and sufficient iced water to make the volume up to 150 ml. The colour change was taken to a fixed shade, and corresponding controls of the same colour required 0·02 ml. of 0·01N-iodine to 0·15 ml. of 0·001N-solution. This procedure was also adopted when standardising the thiosulphate against potassium iodate.

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[9] Davies and Monk, *J.*, 2718, 1951.
[9] Moelywn-Hughes, "Kinetics of Reactions in Solution," Clarendon Press, Oxford, 1947, p. 70.
[10] Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 277.

284. *The Solvolysis of* n-*Propyl Bromide in Aqueous Ethanol.*

By J. R. Bevan and C. B. Monk.

The solvolysis of *n*-propyl bromide in 44% ethanol, both alone and with added bromide, has been followed. There is no salt effect. From temperature effects the energy of activation has been calculated.

The reactions of *n*-propyl bromide in aqueous ethanol consist mainly in the replacement of bromine by hydroxyl and ethoxide groups. Two other possible reactions are :

$$CH_3{\cdot}CH_2{\cdot}CH_2Br \longrightarrow CH_3{\cdot}CH{:}CH_2 + H^+ + Br^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

$$CH_3{\cdot}CH_2{\cdot}CH_2Br \longrightarrow CH_3{\cdot}CH_2{\cdot}CH_2^+ + Br^- \xrightarrow{H_2O} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}OH + H^+$$
$$\xrightarrow{EtOH} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}OEt \quad . \quad . \quad . \quad (b)$$

Bateman and Hughes [1] have shown that mechanism (*a*) is negligible with straight-chain alkyl halides in acidic solutions; the unimolecular mechanism for reaction (*b*) is also negligible [2] with these halides. The reaction is therefore uncomplicated, and in the presence of a large excess of solvent is pseudounimolecular; and it is ideal for testing whether or not there are salt effects since the ionic strength gradually increases as the reaction proceeds, hydrobromic acid being highly dissociated in aqueous ethanol.[3] By addition of magnesium bromide, which is also completely dissociated (as judged by conductivity data [4]) in the solvent used, namely, 44% (w/w) aqueous ethanol, ionic strengths up to 0·14 were developed. An example is given in Table 1.

Table 1. *Solvolysis of* 0·05M-n-*propyl bromide in* 44·05% *ethanol at* 50°.

t (min.)	Ml. of 0·1N-$AgNO_3$ (x)	log [∞/($\infty - x$)]	I	10^6k (sec.$^{-1}$)	t (min.)	Ml. of 0·1N-$AgNO_3$ (x)	log [∞/($\infty - x$)]	I	10^6k (sec.$^{-1}$)
3045	2·152	0·1151	0·01211	1·451	9945	5·345	0·3754	0·03007	1·449
4230	2·872	0·1617	0·01616	1·467	11,400	5·823	0·4322	0·03277	1·455
5910	3·731	0·2247	0·02099	1·459	∞	9·230	—	—	—
8485	4·814	0·3198	0·02710	1·447	∞	9·236	—	—	—

Table 2. *Average values of the velocity constant* (*mole* $l.^{-1}$ *sec.*$^{-1}$) *at* 50°.

[*n*-Propyl bromide]	0·05M	0·10M	0·10M + 0·025M-$MgBr_2$
10^6k	1·453, 1·450	1·437, 1·442	1·416, 1·410

The average value of k together with the values from other runs is given in Table 2, and within the limits of experimental error the reaction shows no salt effects. The mean value at 50° and other temperatures is :

10^6k	1·44	2·37	4·04	9·58
Temp.	50°	55°	60°	70°

From the slope of the plot of log k against $1/T$, which is linear, a mean activation energy of 21·2 ± 0·2 kcal./mole is obtained. From this, the constant A in the Arrhenius equation is $1{\cdot}5 \times 10^9$. The same value was obtained by Moelwyn-Hughes [5] for the hydrolysis of ethyl iodide in water, while Taylor [6] obtained $1{\cdot}4 \times 10^9$ for the solvolysis of *iso*propyl bromide in 60% ethanol.

Experimental

The reaction was studied in sealed tubes since both solvent and solute are volatile at 50°. Moelwyn-Hughes [7] has shown that in the hydrolysis of the methyl halides in water there is a rate difference of 10% between reactions carried out in the presence of a small vapour phase

[1] Bateman and Hughes, *J.*, 1940, 903.
[2] Hughes and Ingold, *J.*, 1940, 932.
[3] Goldschmidt and Dahl, *Z. phys. Chem.*, 1924, **108**, 121.
[4] Unpublished results.
[5] Moelwyn-Hughes, *J.*, 1933, 1576.
[6] Taylor, *J.*, 1937, 992.
[7] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1953, *A*, **220**, 386.

and in its absence. For the present work, soft-glass test-tubes were drawn out to give bulbs of about 21 ml. capacity with a neck sufficiently wide before sealing to allow entry of a 20 ml. pipette for introducing the samples. The free space above the liquid after sealing was 3—4% of the total volume. Since *n*-propyl bromide has b. p. 72°, no significant error is likely from the small vapour phase.

A stock solution was made at 15°, 20 ml. being placed in each bulb, which was then sealed and placed in ice. Four of the tubes, which were of Pyrex glass, were placed in boiling water till solvolysis was complete. The reactions of the others were started by placing them in boiling water for a predetermined time requisite to bring them to 50°, then in a thermostat at 50° ± 0·02°. Tubes were withdrawn at intervals, cooled in ice, and opened, and the contents were washed into flasks and titrated for bromide by Volhard's method. 2 ml. of Volhard's indicator were added, followed by excess of 0·1N-silver nitrate from a microburette. Titration with thiocyanate to the red end-point was followed by addition of excess of thiocyanate and titration with silver nitrate. This gave a check on the end-point; the deviation was <0·005 ml. of 0·1N-silver nitrate.

The reverse reaction was proved to be absent by heating a mixture 0·1M in *n*-propyl alcohol and in hydrobromic acid for 6 days at 50° in the same solvent.

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285. *Thermochemistry of Organophosphorus Compounds. Part II.* Triethyl Phosphate, Tripropylphosphine Oxide, and Tributylphosphine Oxide.*

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Values are reported for the heats of oxidation by hydrogen peroxide (dissolved in methanol) of tripropylphosphine and of tributylphosphine to the phosphine oxides. The heat of oxidation of triethyl phosphite to phosphate, measured similarly, was appreciably higher than the heat given by reaction of triethyl phosphite with aqueous (5%) hydrogen peroxide; in the latter, however, it seems that the oxidation is in competition with hydrolysis.

The thermal data have been used to derive the dissociation energies $D(O{=}PPr_3) \sim 138{\cdot}3$ kcal./mole, $D(O{=}PBu_3) \sim 137{\cdot}2$ kcal./mole, and $D[O{=}P(OEt)_3] \sim 150{\cdot}8$ kcal./mole. Comment is made on the apparent variability in the $O{=}PR_3$ bond dissociation energies with changes in the atom or group R, and some of the factors that may be responsible for these variations are discussed.

THE trialkylphosphines are readily oxidized to their corresponding oxides by various oxidizing agents; *e.g.*, Davies and Jones [1] mention specifically nitric acid, potassium permanganate, peracetic acid, and hydrogen peroxide. The last seemed most suitable for the present studies, as its heat of formation is already well established, and the reactions $R_3P + H_2O_2 \longrightarrow R_3PO + H_2O$ take place rapidly at room temperature in methanol. The oxidation of triethyl phosphite to phosphate by hydrogen peroxide in methanol also takes place readily, and appeared suitable for thermochemical study.

EXPERIMENTAL

Compounds.—Tri-*n*-propylphosphine and tri-*n*-butylphosphine were prepared according to Davies and Jones [1] and Davies, Pearse, and Jones,[2] by reaction of phosphorus trichloride with the appropriate Grignard reagents. The crude products were fractionally distilled under reduced (nitrogen) pressure, through an 8″ gauze-packed column. The tri-*n*-propylphosphine

* Part I, *J.*, 1955, 3936.

[1] Davies and Jones, *J.*, 1929, 33.
[2] Davies, Pearse, and Jones, *J.*, 1929, 1262.

fraction (b. p. 74—75°/6·5 mm.) and the tri-*n*-butylphosphine fraction (b. p. 110—111°/10 mm.) were retained, redistilled *in vacuo*, and collected and sealed in thin glass ampoules. Triethyl phosphite was prepared as described in Part I. Tri-*n*-propylphosphine oxide was made by oxidation of the phosphine with hydrogen peroxide in methanol; the resulting solution was fractionally distilled, and the fraction (b. p. 262°/750 mm.) retained. Tri-*n*-butylphosphine oxide was prepared similarly (b. p. 293—296°/745 mm.). Both oxides are colourless solids at room temperature, and are very hygroscopic.

Calorimeter.—The calorimeter was that described in Part I. The oxidation reactions were carried out by breaking ampoules, containing known weights of reactant, into 750 c.c. of methanol in which a small amount of hydrogen peroxide was dissolved. The resulting temperature rise was followed by the change in resistance of a shielded thermistor element. A slow stream of nitrogen (saturated with methanol vapour) was maintained during each experiment in the head-piece fitting the Dewar vessel, to prevent oxidation by air; also the methanol was alternately degassed and saturated with nitrogen, until rid of dissolved oxygen, before use in the calorimeter. The hydrogen peroxide consumed was determined volumetrically: a known excess of ceric ammonium sulphate solution was added to aliquot samples of the initial methanol–hydrogen peroxide solution and of the final calorimeter contents: the excess of ceric ion was back-titrated against ferrous ammonium sulphate solution, ferroin being used as indicator. The ferrous ammonium sulphate solution was standardized against potassium dichromate solution.

Units.—All heat quantities are given in units of the thermochemical calorie, defined as 1 cal. ≡ 4·1840 abs. joule. The experiments were performed at 25°.

Results.—(a) *Oxidation of tri-n-propylphosphine.* The methanol–hydrogen peroxide solution contained 1·7 ml. of hydrogen peroxide (110-vol.) per l. of methanol. Nine measurements of the heat of oxidation of propylphosphine were made; the purity of the phosphine, determined from the hydrogen peroxide consumption, was 97—99%. The observed heats of reaction ($\Delta H_{obs.}$) refer to the equation:

$$PPr_3 \text{ (liq.)} + H_2O_2{,}4{\cdot}7H_2O \text{ (methanol soln.)} \longrightarrow OPPr_3 + 5{\cdot}7H_2O \text{ (methanol soln.)} \quad . \quad (1)$$

A representative selection from the values of $\Delta H_{obs.}$ is given in Table 1; the values are based on the hydrogen peroxide consumed, and not on the weight of phosphine used. The limits of error to be attached to the mean $\Delta H_{obs.}$ we estimate at *ca.* ±2 kcal./mole, arising from possible errors of *ca.* 1% in the volumetric analysis, and errors of similar order in the calorimetry.

TABLE 1. *Heat of oxidation of tri-n-propyl phosphine.*

PPr_3 (mmoles)	H_2O_2 used (mmoles)	Purity (%) of PPr_3	$-\Delta H_{obs.}$ (kcal./mole)	PPr_3 (mmoles)	H_2O_2 used (mmoles)	Purity (%) of PPr_3	$-\Delta H_{obs.}$ (kcal./mole)	
4·161	4·095	98·4	107·9	4·420	4·367	98·8	108·2	Mean value, $\Delta H_{obs.}$
3·710	3·629	97·8	109·3	4·289	4·177	97·4	106·9	= −108·1

The heat of solution of solid tri-*n*-propylphosphine oxide in methanol * was measured separately, $\Delta H_{soln.} = -1{\cdot}32$ kcal./mole. The heat of solution of hydrogen peroxide (110-vol.) in methanol was barely distinguishable (at the concentrations used in the oxidation studies) from that of water in methanol. Accordingly, we may obtain, for the idealized reaction:

$$PPr_3 \text{ (liq.)} + H_2O_2 \text{ (liq.)} \longrightarrow OPPr_3 \text{ (c.)} + H_2O \text{ (liq.)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$\Delta H = -106{\cdot}8$ (±2) kcal./mole. Accepting the values, $\Delta Hf°$ (H_2O, liq.) = −68·3 kcal./mole, and $\Delta Hf°$ (H_2O_2, liq.) = −45·7 kcal./mole (N.B.S. Tables, Circular 500), we have from eqn. (2) the *difference* $\Delta Hf°(OPPr_3, c.) - \Delta Hf°(PPr_3, liq.) = -84{\cdot}2$ (±2) kcal./mole.

(b) *Oxidation of tri-n-butylphosphine.* Six measurements of the heat of oxidation of tributylphosphine were made, from which the mean value $\Delta H_{obs.} = -107{\cdot}0$ kcal./mole resulted. The determinations of purity, from the hydrogen peroxide consumption, were less consistent than in the tripropylphosphine oxidations, although all (except one) were 97—100% pure. We accordingly assign slightly larger error limits (±3 kcal./mole) to $\Delta H_{obs.}$ in the present case.

The heat of solution of tri-*n*-butylphosphine oxide in methanol was measured separately, $\Delta H_{soln.} = -1{\cdot}29$ kcal./mole. Hence, for the idealized reaction,

$$PBu_3 \text{ (liq.)} + H_2O_2 \text{ (liq.)} \longrightarrow OPBu_3 \text{ (c.)} + H_2O \text{ (liq.)} \quad . \quad . \quad . \quad . \quad (3)$$

$\Delta H = -105{\cdot}7$ (±3) kcal./mole, and the *difference* $\Delta Hf°$ ($OPBu_3$, c.) − $\Delta Hf°$ (PBu, liq.) = −83·1 (±3) kcal./mole.

* The methanol contained a little water—to comply with the conditions represented by eqn. (1).

(c) *Oxidation of triethyl phosphite.* Preliminary measurements on the heat of oxidation of triethyl phosphite were carried out with *aqueous* hydrogen peroxide as oxidant. The experimental conditions were essentially the same as those described by Neale and Williams.[3] The heat of oxidation, when 5% aqueous hydrogen peroxide was used, was found to be ΔH = −99·2 kcal./mole.

However, in aqueous hydrogen peroxide, the oxidation of ethyl phosphite takes several minutes to approach completion, owing to the slowness of the solution of the phosphite in water. The possibility that some triethyl phosphite might be lost during this time through competing hydrolytic reactions could not be disregarded. The secondary ester, which is formed by hydrolysis, exists in the keto-form, H·PO(OEt)$_2$, with the phosphorus atom already in the quinquevalent state, so that it is not readily oxidized. Hence it may be that the heat measured when using aqueous hydrogen peroxide is composite, in part arising from the phosphite ⟶ phosphate oxidation, and in part from hydrolysis of the tertiary phosphite.

Arbuzov [4] and Arbuzov, Zoroastrova, and Rizpolozhenskii [5] have stated that triethyl phosphite is stable in pure water, but is hydrolysed quite rapidly in the presence of dilute acids. Two experiments were carried out to ascertain whether or not hydrolysis occurred in the calorimeter under the conditions of the aqueous oxidation experiments. First, a sample of triethyl phosphite was broken into 750 ml. of aqueous hydrochloric acid, in the calorimeter, and the time–resistance graph was plotted for 2 hr. afterwards. There was an initial rapid resistance change, followed by a much slower one, after which the plot straightened out; the overall heat change was of the order 17 kcal. per mole of triethyl phosphite added. In the second experiment a similar sample of triethyl phosphite was broken into 750 ml. of conductivity water. In this case the resistance change occurred more slowly, but the overall change after 2 hr. was again similar (ΔH = −17 kcal./mole). The heat evolved is appreciably larger than to be expected from a mere heat of solution effect, and indicates that hydrolysis occurs both in acid and in neutral solution, although less rapidly in the latter.

Because of the possible complications due to hydrolysis in the aqueous oxidations, the oxidation by hydrogen peroxide in methanol was chosen for further study. Since triethyl phosphite is easily soluble in methanol, the reaction occurs far more rapidly in this medium, and it was now possible to use very dilute hydrogen peroxide. The procedure was that described for the oxidation of tripropylphosphine. In most cases, samples of phosphite were broken into methanol–hydrogen peroxide solution containing an excess of peroxide (relative to added phosphite), and the amount of peroxide used was estimated volumetrically. The reverse procedure (excess of phosphite into peroxide) was followed in a few cases. Finally, some experiments were done using dry methanol (dehydrated with magnesium methoxide) in which a small amount of 90% hydrogen peroxide was dissolved; these may conveniently be termed " water-free " conditions.

Nine experiments were made in the calorimeter, the first four with a sample of ethyl phosphite which was made without special precautions against atmospheric oxidation. Subsequent infrared analysis of this batch sample showed it to contain *ca.* 5% of impurity (ethyl phosphate); correspondingly, with samples from this batch, the hydrogen peroxide consumed was found to be low (94—96%) on the weight of phosphite taken. A second batch, prepared under nitrogen, gave purity figures of 98—100% on hydrogen peroxide consumption, and the infrared analysis

TABLE 2. *Oxidation of triethyl phosphite.*

$P(OEt)_3$ (mmoles)	Purity (%) from H_2O_2 used	$-\Delta H_{obs.}$* (kcal./mole)	Comments
6·330	96·3	116·3	Excess of 30% H_2O_2 in methanol
5·476	98·2	116·1	" "
4·986	100	115·9	" "
5·103	100	115·4	" Water-free "
5·928	100	117·8	H_2O_2 (30%) added to excess of phosphite

Mean $\Delta H_{obs.}$ = − 116·3 kcal./mole.

* Corrected for the heat of solution in methanol of the water contained in the 30% H_2O_2 added.

confirmed less than 2% of ethyl phosphate as impurity. A selection from the results obtained is given in Table 2.

The heat of solution of liquid ethyl phosphate in methanol was measured separately and

[3] Neale and Williams, *J.*, 1955, 2485.
[4] Arbuzov, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 291.
[5] Arbuzov, Zoroastrova, and Rizpolozhenskii, *Izvest. Akad. Nauk, S.S.S.R.*, 1948, 208.

found to be small ($\Delta H_{soln.}$ = 0·1 kcal./mole); for ethyl phosphite in methanol, $\Delta H_{soln.}$ = 1·0 kcal./mole. Thus, for the idealized reaction,

$$P(OEt)_3 \text{ (liq.)} + H_2O_2 \text{ (liq.)} \longrightarrow OP(OEt)_3 \text{ (liq.)} + H_2O \text{ (liq.)} \quad . \quad . \quad . \quad . \quad (4)$$

the heat of reaction is unchanged from $\Delta H_{obs.}$ of Table 2, and the difference $\Delta Hf°[OP(OEt)_3, \text{liq.}] - \Delta Hf°[P(OEt)_3, \text{liq.}] = -93·7$ kcal./mole. The limits of error in $\Delta H_{obs.}$ we estimate at *ca.* ±2 kcal./mole. With the value given in Part I, $\Delta Hf°[P(OEt)_3, \text{liq.}] = -204·1$ kcal./mole, we obtain $\Delta Hf°[OP(OEt)_3, \text{liq.}] = -297·8$ kcal./mole.

Discussion

The heat of dissociation of a molecule OPR_3 in the gaseous phase, $OPR_3(g.) \longrightarrow O(g.) + PR_3(g.)$, is given by the thermochemical equation :

$$D(O{=}PR_3) = \Delta Hf°[PR_3, g.] - \Delta Hf°[OPR_3, g.] + \Delta Hf°[O, g.] \quad . \quad . \quad . \quad . \quad (5)$$

For the molecules R = OEt, the heats of vaporization of both PR_3 and OPR_3 have been reported :[6] $\Delta H_{vap.}[P(OEt)_3] = 10·0$ kcal./mole, $\Delta H_{vap.}[OP(OEt)_3] = 12·0$ kcal./mole, so that we obtain $\Delta Hf°[P(OEt)_3, g.] - \Delta Hf°[OP(OEt)_3, g.] = 91·7$ kcal./mole. As the value $\Delta Hf°(O, g.) = 59·1$ kcal./mole is well established (N.B.S. Tables, Circular 500), eqn. (5) then gives the value $D[O{=}P(OEt)_3] = 150·8$ kcal./mole.

Heats of vaporization for propyl- and butyl-phosphine and -phosphine oxide have not been reported, but, from the boiling points and Trouton's constant the difference in the heats of vaporization of the phosphine oxides and the phosphines may be estimated at *ca.* 2 kcal./mole. The heats of fusion of the phosphine oxides are also undetermined; an estimate of *ca.* 3 kcal./mole cannot be seriously in error, however. Thus we may derive $D(OP{=}Pr_3) \sim 138·3$ kcal./mole, and $D(O{=}PBu_3) \sim 137·2$ kcal./mole; these values may be unreliable within limits of *ca.* ±4 kcal./mole, allowance being made for possible errors in the thermochemistry, coupled with the assumptions made in respect of the heats of vaporization and fusion.

The O=P< dissociation energies now reported are higher than those in the phosphorus oxyhalides,[7] and it seems that $D(O{=}PR_3)$ values may vary appreciably with changes in the atom or group R. We are unable to give a detailed explanation for the apparent variability in $O{=}PR_3$ bond dissociation energies, but the problem is not easy, since the dissociation process is accompanied by a change in the valency state of the phosphorus atom, so that some reorganization in the PR_3 part of the OPR_3 molecule is likely to occur on dissociation.

In the cases R = Cl or F, the structural parameters in both PR_3 and OPR_3 are accurately known from studies in the microwave spectral region,[8] and on dissociation of $OPHal_3$, we now know that the P–Hal bond lengths increase slightly, whilst the Hal–P–Hal angles diminish. Although these changes are not large, they may well involve a reorganization energy of significant magnitude. The structural parameters in PR_3 and OPR_3, where R = OEt, Pr, or Bu, are not known.

The P=O bond length in OPF_3 and in $OPCl_3$ is 1·45 Å,[8c] and is the same as found in the ground-state, $^2\Pi$, of the diatomic PO molecule (r_e = 1·447 Å; Herzberg [9]) for which Gaydon [10] quotes the dissociation energy as 143 ± 12 kcal./mole. This bond length is even shorter than that observed in the ground-state, $^1\Sigma^+$, of the PN molecule (r_e = 1·491 Å), in which it is reasonable to suppose there is a triple bond, P≡N. The formulation $O{=}PHal_3$, in which the oxygen–phosphorus linkage is represented as a double bond, is thus not altogether satisfactory. We prefer to regard the OPR_3 molecule as one in which the tetrahedral structure, $\bar{O}$–$\overset{+}{P}R_3$, is modified by back-co-ordination from the $2p_x^2$ and $2p_y^2$ orbitals of $\bar{O}$ to the (vacant) $3d_e$ orbitals of P^+ (thus giving $\bar{O}$–$\overset{+}{P}$ triple-bond character), with the further

[6] Evans, Davies, and Jones, *J.*, 1930, 1310.
[7] Charnley and Skinner, *J.*, 1953, 450; Neale and Williams, *J.*, 1954, 2156.
[8] (*a*) Gillam, Edwards, and Gordy, *Phys. Rev.*, 1949, **75**, 1014; (*b*) Kisluik and Townes, *J. Chem. Phys.*, 1950, **18**, 1109; (*c*) Williams, Sheridan, and Gordy, *ibid.*, 1952, **20**, 164.
[9] Herzberg, "Molecular Spectra and Molecular Structure, I, Diatomic Molecules," 2nd Edn., Van Nostrand, New York, 1950.
[10] Gaydon, "Dissociation Energies," 2nd Edn., Chapman and Hall, London, 1953.

possibility, in case that R_3 possesses donor electrons, of weaker back-co-ordination to P^+ from the R_3 group (cf. Kimball [11]). The stability of the OPR_3 molecule should, in this event, depend to some extent on the propensity of the atom or group R to act as a donor. Skinner and Smith [12] have previously suggested that the OEt group is more powerful in back-co-ordination than is the Cl atom, and this might be one factor responsible for the increase in D[O=P(OEt)$_3$] over D(O=PCl$_3$). It is, however, difficult to explain in these terms why the bond dissociation energies in the alkylphosphine oxides should be larger than in the phosphorus oxyhalides.

In conclusion, we draw attention to an important assumption made in interpreting most of the results given here, namely, that hydrogen peroxide is consumed *only* in accordance with the equation $R_3P + H_2O_2 \longrightarrow R_3PO + H_2O$. This assumption has not been experimentally verified by us, and objection could be raised against our conclusions on this account. There is the possibility, *e.g.*, that small amounts of phosphine peroxides, R_3PO_2, which have been reported by various workers,[13] are formed, which might analyze as unchanged hydrogen peroxide and thus escape detection. An attempt to eliminate this possibility by some further experiments, in which *excess* of phosphine was added to hydrogen peroxide in methanol was unsuccessful, and the measured heats of reaction under these conditions were not reproducible. In our opinion, the thermochemical results given here need independent verification, possibly by oxidation studies based on some other agent than hydrogen peroxide.

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[11] Kimball, *J. Chem. Phys.*, 1940, **8**, 188.
[12] Skinner and Smith, *J.*, 1954, 2324, 3930.
[13] Jorissen, *Z. phys. Chem.*, 1897, **22**, 35; Engler and Weissberg, *Ber.*, 1898, **31**, 3055; Thompson and Kelland, *J.*, 1933, 1231.

286. *The Dipole Moments of Pyridine, Quinoline, and* iso*Quinoline as Vapours and as Solutes.*

By A. D. Buckingham, J. Y. H. Chau, H. C. Freeman, R. J. W. Le Fèvre, D. A. A. S. Narayana Rao, and J. Tardif.

Determinations of the polarisations of the substances named in the title as vapours reveal limitations in accuracy of the conventional experimental arrangements. New measurements of the dipole moments of these liquids as solutes in light petroleum, carbon tetrachloride, or benzene show that quinoline and *iso*quinoline conform within $\pm 3\%$ to an empirical equation advanced by Buckingham and Le Fèvre, the second liquid doing so more satisfactorily than the first. The $\mu_{soln.}/\mu_{gas}$ ratios found for pyridine are notably higher than expected. This behaviour may be attributed in part to association with the solvents: thus pyridine and carbon tetrachloride could tend to form a quaternary polar complex; alternatively $_AP_{C_6H_5N}$ might be increased as an effect of solvation. In either case the moment—and hence the quotient $\mu_{soln.}/\mu_{gas}$—recorded by use of the refractivity method applied to solutions would appear to be larger than that forecast by previously adequate relations.

The measurements here recorded, commenced several years ago, were to provide critical data for the comparison of various equations by which the "true" or gas-phase dipole moments of molecules could be predicted from experiments on solutions. It seemed that three solutes—pyridine, quinoline, and *iso*quinoline—offered interesting differences in shape-factors although their polarities were roughly the same.

As no figures for the three "gas" moments were available, determinations of the polarisations of the vapours at temperatures from 90° to 315° were undertaken. The observations listed below were made by several of the authors at widely separated intervals.

The order of their accuracy is not so high as it was hoped to achieve. The technical difficulties incurred in making the polarisation measurements at high temperatures, and the uncertainties inherent in the calibration of the apparatus, are considered in detail below.

In addition, earlier determinations of the electric moments of the three substances in benzene have been supplemented; and new ones have been made in light petroleum and carbon tetrachloride. These results are summarised in Table 1.

TABLE 1. *Dipole moments and* $\mu_{soln.}/\mu_{gas}$ *ratios for pyridine, quinoline, and* isoquinoline.*

Substance	$\mu_{l.p.}$†	μ_{CCl_4}	$\mu_{C_6H_6}$	μ_{gas}	$\mu_{l.p.}/\mu_{gas}$	μ_{CCl_4}/μ_{gas}	$\mu_{C_6H_6}/\mu_{gas}$
Pyridine	2·27	2·37	2·25	2·23 (0·02)	1·02 (0·02)	1·06 (0·02)	1·01 (0·02)
Quinoline	2·17	2·27	2·24	2·29 (0·05)	0·95 (0·06)	0·99 (0·06)	0·98 (0·06)
*iso*Quinoline	2·60	2·65	2·61	2·73 (0·03)	0·95 (0·04)	0·97 (0·04)	0·96 (0·04)

* Figures in parentheses following μ_{gas} are standard deviations calculated from observations. Estimates of the standard deviations of the quotients have been made by assuming those of the solution moments to be ± 1% of the values tabulated.
† "l.p." = light petroleum.

EXPERIMENTAL

Polarisations of Vapours.—For the vapours of pyridine, quinoline, and *iso*quinoline we used the high-temperature oven–Franklin oscillator–wavemeter combination.[1] For one series of measurements on pyridine, the apparatus was calibrated with sulphur dioxide. The quantity $x' = (\partial C/p)_{p\to 0}$ for this substance at any temperature was obtainable from an experimental curve, $x' = (241{\cdot}15/T - 0{\cdot}2095)$, and the polarisation[2] $P_{SO_2} = 10{\cdot}9 + 16160/T$.

For the other two substances, and for a second sequence of measurements on pyridine, benzene was taken as the standard gas. Using dry air with ${}_{\gamma}P = 4{\cdot}344$ c.c. as a primary standard,[3] we found the average polarisation of benzene vapour at those temperatures to be 27·2 ± 0·2 c.c. The standard deviations of the constants in the Debye equations were computed.[4]

TABLE 2. *Polarisations of vapours.*

Temp. (°K)	x/x'	No. of obsns.	Press. range (cm. Hg)	P (c.c.) (msd.)	P (c.c.) (calc.)	μ *	Temp. (°K)	x/x'	No. of obsns.	Press. range (cm. Hg)	P (c.c.) (msd.)	P (c.c.) (calc.)	μ *
					Pyridine †								
414·7	1·868	13	16—60	93·2	93·4	—	539	1·866	15	18—60	76·3	76·1	—
428·1	1·847	14	15—62	89·8	91·0	—	562	1·841	15	19—62	73·1	73·7	—
477·4	1·902	19	14—62	85·2	83·5	—	588	1·831	19	15—59	70·3	71·3	—
518	1·891	16	20—61	79·6	78·4	—							

whence $P = (18{\cdot}4 \pm 3{\cdot}6) + (31{,}090 \pm 1630)/T$; $\mu = 2{\cdot}26 \pm 0{\cdot}06$ D.

		Pyridine ‡ (R_D = 24·1 c.c.)						*Quinoline* ‡ (R_D = 41·9 c.c.)					
365	3·863	5	6—13	105·1	104·7	2·20	482	3·945	10	5—7	107·3	110·1	2·27
431	3·374	5	6—11	91·8	92·0	2·19	498	3·961	11	7—8	107·8	107·1	2·32
439	3·319	6	6—11	90·3	90·7	2·18	499	3·999	9	3—7	108·8	106·9	2·34
499	3·036	6	6—8	82·6	82·5	2·19	521	3·832	11	5—10	104·4	103·0	2·31
542·5	2·864	5	14—21	77·9	77·6	2·19	572	3·447	15	4—9	93·8	95·1	2·21

whence $P = (22{\cdot}0 \pm 1{\cdot}3) + (30{,}175 \pm 590)/T$; $\mu = 2{\cdot}23 \pm 0{\cdot}02$ D (For pyridine).
Debye equation: $P = (14{\cdot}2 \pm 17{\cdot}7) + (46{,}270 \pm 9100)/T$; $\mu = 2{\cdot}8 \pm 0{\cdot}3$ D (For quinoline).
Refractivity method: $\mu = 2{\cdot}29 \pm 0{\cdot}05$ D (For quinoline).

					*iso*Quinoline ‡ (R_D = 41·5 c.c.)								
448	5·246	9	1—2	142·6	144·3	2·73	513	4·774	11	4—8	129·9	130·0	2·73
469	5·247	9	4—6	142·7	139·2	2·79	513	4·737	9	1—9	128·8	130·0	2·71
492	4·980	6	4—7	135·5	134·2	2·76	547	4·667	11	5—10	126·9	123·8	2·77
494	4·809	8	1—3	130·6	133·7	2·69	565	4·459	11	8—13	121·3	120·9	2·71
497	4·974	12	5—8	135·3	133·1	2·76	567	4·368	11	7—20	118·8	120·9	2·68

Debye equation: $P = (31{\cdot}6 \pm 32{\cdot}6) + (50{,}650 \pm 16{,}540)/T$; $\mu = 2{\cdot}9 \pm 0{\cdot}5$ D.
Refractivity method: $\mu = 2{\cdot}73 \pm 0{\cdot}03$ D.

* By refractivity method. † Standard vapour: SO_2. ‡ Standard vapour: benzene.

[1] Freeman, Le Fèvre, Rao, and Ross, *J.*, 1955, 3840.
[2] Le Fèvre, Ross, and Smythe, *J.*, 1950, 267.
[3] Le Fèvre, "Dipole Moments," Methuen, London, 3rd edn., 1953, p. 45.
[4] Cf., *e.g.*, Youden, *Analyt. Chem.*, 1947, **19**, 946.

The results are shown in Table 2. For pyridine, the two series of determinations gave Debye equations which were compatible with each other within the standard errors of their A and B terms. The measurements with benzene as standard were more self-consistent and hence the value $\mu = 2{\cdot}23 \pm 0{\cdot}02$ D will be taken for the true dipole moment of pyridine.

From the experimental standpoint, the temperature ranges over which the measurements could be made were limited by the b. p.s of the substances on the one hand and by the instability of vacuum-greases, glass diaphragms, and electric connections on the other. For quinoline and *iso*quinoline, these conditions restricted measurements to ranges of *ca.* 100° : extrapolation from such short temperature ranges gave standard deviations of ${}_{\mathrm{D}}P$, in the Debye equations,

TABLE 3. *Dielectric constants and densities of solutions.*

$10^4 w_2$	ε_{25}	d_4^{25}	$10^4 w_2$	ε_{25}	d_4^{25}	$10^4 w_2$	ε_{25}	d_4^{25}
			Pyridine in light petroleum					
1043	1·9805	0·6981	1883	2·0212	0·7004	3940	2·1307	0·7037
1248	1·9913	0·6982	1958	2·0273	0·6995	4247	—	0·7041
1411	2·0017	0·6985	2444	2·0522	0·7006			
			Pyridine in carbon tetrachloride					
543	2·3024	1·57955	1127	2·3845	1·57429	1858	2·4843	1·56755
1002	2·3658	1·57523	1702	2·4641	1·56882	2029	1·5078	1·56554
			Pyridine in benzene					
993	2·3420	0·87384	2891	2·4749	0·87684	6081	2·6982	0·88019
1361	2·3660	0·87529	4988	2·6217	0·87904	6935	2·7579	0·88108
1877	2·4039	0·87578						
			Quinoline in light petroleum					
931	1·9583	0·6982	1581	1·9767	0·6999	3201	2·2076	0·7042
1087	1·9626	0·6985	1965	1·9896	0·7008	3575	2·0409	0·7052
1151	1·9659	0·6986	2625	2·0109	0·7027	3893	2·0507	0·7061
			Quinoline in carbon tetrachloride					
859	2·2986	1·57829	1261	2·3313	1·57575	1663	2·3645	1·57293
892	2·3011	1·57818	1422	2·3430	1·57487	1789	2·3738	1·57184
			Quinoline in benzene					
561	2·2980	0·8747	1875	2·3585	0·8773	3106	2·4161	0·8794
797	2·3070	0·8755	1952	2·3585	0·8775	3169	2·4165	0·8799
898	2·3143	0·8753	1954	2·3656	0·8776	3506	2·4092	0·8802
1041	2·3208	0·8756	2926	2·4055	0·8794	3557	2·4353	0·8805
			*iso*Quinoline in light petroleum					
914	1·9705	0·6983	1946	2·0118	0·7010	4230	2·1103	0·7073
1511	1·9943	0·6998	2133	2·0180	0·7015	4293	2·1096	0·7074
1813	2·0065	0·7006	2150	2·0185	0·7016	5261	2·1539	0·7100
			*iso*Quinoline in carbon tetrachloride					
797	2·3144	1·58398	1261	2·3660	1·58371	1659	2·4104	1·57352
853	2·3206	1·58394	1365	2·3774	1·57594	2430	2·4951	1·56806
			*iso*Quinoline in benzene					
610	2·3089	0·87504	896	2·3264	0·87558	1017	2·3338	0·87588
780	2·3204	0·87538	989	2·3320	0·87579	2233	2·4087	0·87830

TABLE 4. *Calculation of results from solutions.*

Solute	Solvent	$\alpha\varepsilon_1$ (mean)	β (mean)	${}_{\infty}P_2$ (c.c.)	R_{D} (c.c.)	μ (D)
Pyridine	L. p.	4·99	0·284	129·3	24·1	$2{\cdot}2_7$
,, ...	CCl_4	13·84	−0·583	138·8	,,	$2{\cdot}3_7$
,, ...	C_6H_6	6·99	0·117	127·8	,,	$2{\cdot}2_5$
Quinoline	L. p.	$3{\cdot}06_5$	0·367	138·3	41·9	$2{\cdot}1_7$
,, ...	CCl_4	8·25	−0·443	147·1	,,	$2{\cdot}2_7$
,, ...	C_6H_6	4·48	0·214	144·4	,,	$2{\cdot}2_4$
*iso*Quinoline	L. p.	4·22	0·382	179·3	41·5	$2{\cdot}6_0$
,, ...	CCl_4	11·01	−0·424	184·4	,,	$2{\cdot}6_3$
,, ...	C_6H_6	6·06	0·233	181·0	,,	$2{\cdot}6_1$

which exceeded the numerical values of ${}_{D}P$ obtained. For these compounds, the dipole moments were calculated *via* the orientation polarisations, taken as $({}_{T}P - R_{D})$.

Solution Measurements.—A new apparatus for the measurement of the dielectric constants of liquids has been constructed to replace those described in *J.*, 1948, 1949, and *J.*, 1953, 1626. Circuit details are shown in the Figure. The arrangement is a less sensitive version of that developed for gases by Le Fèvre, Ross, and Smythe (ref. 2, Fig. 3). The test cells and standard (Sullivan 50—250 $\mu\mu$F) variable condenser C, used formerly, have been retained. The reference

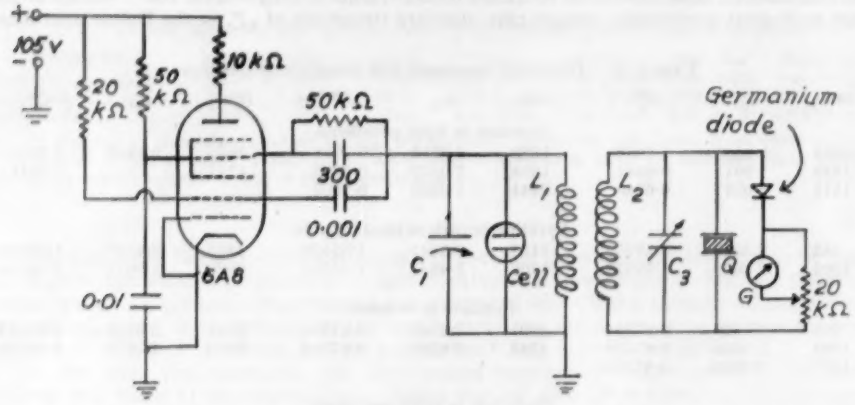


TABLE 5. *Comparison of present data with those from earlier literature.*

Solvent	Temp.	${}_{\infty}P_2$ (c.c.)	${}_{D}P$ (c.c.)	μ(D)	No. of solns. examined	Ref.	Solvent	Temp.	${}_{\infty}P_2$ (c.c.)	${}_{D}P$ (c.c.)	μ(D)	No. of solns. examined	Ref.
							Pyridine						
C_6H_6	24°	*ca.* 114 *	23	2·11	6†	*a*	CCl_4	20°	139·3	?	2·33	?	*e*
							C_6H_6	20	132·6	?	2·26	?	
C_6H_6	15·1	$\infty(_{O}P)$ = 104·5		2·21	4	*b*	C_6H_5Me	20	131·0	?	2·25	?	
							CS_2	20	117·8	?	2·10	?	
C_6H_6		$P = 31·3 + 31{,}420/T$		2·26	?	*c*	C_6H_6	25	125·4	26·5	2·20	3	*f*
							Dioxan	25	127·8	26·5	2·22	4	
C_6H_6	17	130·7	24·54	2·23	?	*d*	L. p.	25	129·3	24·1	2·27	8	*g*
(From P at 3 temperatures)				2·34	—		CCl_4	25	139·1	24·1	2·37	6	
C_6H_{14}	20	127·7	?	2·21	?	*e*	C_6H_6	25	127·8	24·1	2·25	5	
cyclo-Hexane	20	126·5	?	2·20	?								
							Quinoline						
C_6H_6	25	*ca.* 150 *	?	2·25	9†	*h*	C_6H_6	25	141·1	41·9	2·19	4	*j*
								?	?	?	?	2·18	?	*k*
C_6H_6	14·2	$\infty(_{O}P)$ = 97·4		2·14	4	*b*	L. p.	25	138·3	41·9	2·17	9	*g*
							CCl_4	25	147·1	41·9	2·27	6	
C_6H_6	25	141	41·9	2·18	3	*i*	C_6H_6	25	144·4	41·9	2·24	12	
C_6H_6		$P = 39·0 + 28{,}980/T$		2·16	?	*c*							
							*iso*Quinoline						
C_6H_6	14·2	$\infty(_{O}P)$ = 137·5		2·53	4	*b*	C_6H_6	25	175·8	41·5	2·55	4	*j*
							L. p.	25	179·3	41·5	2·60	9	*g*
C_6H_6	25	173·7	41·5	2·52	3	*i*	CCl_4	25	184·4	41·5	2·65	6	
C_6H_6		$P = 41·2 + 39{,}770/T$		2·54	?	*c*	C_6H_6	25	181·0	41·5	2·61	6	

References. (*a*) Lange, *Z. Physik*, 1925, **33**, 169. (*b*) Bergmann, Engel, and Meyer, *Ber.*, 1932, **65**, 446. (*c*) Rau and Narayanaswamy, *Z. phys. Chem.*, 1934, *B*, **26**, 23. (*d*) Goethals, *Rec. Trav. chim.*, 1935, **54**, 299. (*e*) Middleton and Partington, *Nature*, 1938, **141**, 516. (*f*) Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79. (*g*) Present work. (*h*) Rolinski, *Physikal. Z.*, 1928, **29**, 658. (*i*) Le Fèvre and Smith, *J.*, 1932, 2810. (*j*) Le Fèvre and Le Fèvre, *J.*, 1935, 1470. (*k*) Topchiev, Yakshin, and Shindel, *Chem. Abs.*, 1943, **37**, 290.

? = Not stated in source quoted.
* = Estimated by present authors.
† = Complete concentration range from 0—100% covered.

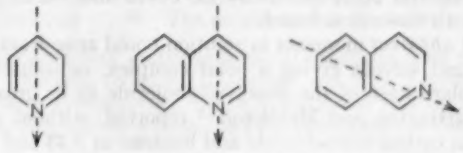
point is the sharp minimum of a current "crevasse."[5] For this reason it is desirable to choose by trial a mounted quartz crystal which exhibits one "crevasse" which is notably deeper than others usually accompanying it. Performance has proved most satisfactory, drift being negligible during several hours.

Observations are tabulated under the usual headings in Table 3. For the three solvents, the necessary physical properties are listed below Table 6. Table 4 shows the calculations of the moments in solution, and Table 5 summarises data from the literature.

Materials.—B.D.H. pyridine was purified *via* the zinc chloride double salt (twice recrystallised from alcohol), and distilled over sodium hydroxide pellets just before use; it had b. p. 115—115·5°/760 mm (Biddiscombe, Coulson, Handley, and Herington[6] give b. p. 115·256°/760 mm.; cf. also Heap, Hones, Speakman[7]). Quinoline (B.D.H. "synthetic") was treated with a diazotising mixture[8] and steam-distilled to remove all volatile material. The mixture was then made alkaline and again steam-distilled. The quinoline after separation was dried (KOH) and fractionated through a 24" column, packed with Fenske helices, under adiabatic conditions. Collection for use was made at 140—143°/*ca.* 50 mm. or 124—125°/25—26 mm. *iso*Quinoline (B.D.H.) was solid at room temperature; it was twice fractionated through the column used for quinoline, the portion with b. p. 117°/15 mm. being retained. Benzene and carbon tetrachloride were purified by methods often described previously.[9] Light petroleum, b. p. *ca.* 80°, was used without further treatment other than drying with sodium.

Discussion

In order to test the several empirical relations between $\mu_{soln.}$ and μ_{gas}, scale drawings were made as described before.[10] They were based on the published dimensions of pyridine



(I) (II) (III)

and naphthalene.[11] The molecular dimensions, together with the assumption[12] that the molecular resultant moments act as indicated in (I), (II), and (III), yielded the geometrical part of the data in Table 6, which shows the ratios $\mu_{soln.}/\mu_{gas}$ predicted by the relations of Barclay and Le Fèvre and of Buckingham and Le Fèvre.[10] Ross and Sack's equation[13] has also been applied since this seems the most satisfactory yet produced of those which rest upon *a priori* theory;[14] the internal field functions ζ have been read from Osborn's graphs of demagnetising factors.[15] Comparison with the predictions of $\mu_{soln.}/\mu_{gas}$ in Table 6 shows the Buckingham–Le Fèvre formula to be applicable within $\pm 3\%$ to quinoline and *iso*quinoline; the three cases involving pyridine display ratios from 6 to 14% larger than those forecast.

We have accordingly considered whether our figures for μ_{gas} of pyridine are too low, or those for $\mu_{soln.}$ too high. The former is improbable: ${}_{D}P$ usually exceeds R_D, so that the use of the correct ${}_{D}P$'s—were they more satisfactorily known—would yield smaller values for μ_{gas} than those of Table 2. We note in this connection that two determinations of $\mu_{pyridine}$ by Stark splitting have been recorded as 2·19 and 2·09 D.[16]

[5] See ref. 3, p. 37.
[6] Biddiscomb, Coulson, Handley, and Herington, *J.*, 1954, 1962.
[7] Heap, Hones, and Speakman, *J. Amer. Chem. Soc.*, 1921, **43**, 1936.
[8] Clarke and Davis, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 478.
[9] See, *e.g.*, Le Fèvre, ref. 3, p. 45.
[10] (*a*) Barclay and Le Fèvre, *J.*, 1950, 556; (*b*) Angyal, Barclay, and Le Fèvre, *J.*, 1950, 3370; (*c*) Buckingham and Le Fèvre, *J.*, 1952, 1932.
[11] Schomaker and Pauling, *J. Amer. Chem. Soc.*, 1939, **61**, 1769; Mathieson, Robertson, and Sinclair, *Acta Cryst.*, 1950, **3**, 245, 257.
[12] Le Fèvre and Le Fèvre, *J.*, 1935, 1470.
[13] Ross and Sack, *Proc. Phys. Soc.*, 1950, **63**, 693.
[14] Cf. Le Fèvre, ref. 3, Chap. III.
[15] Osborn, *Phys. Rev.*, 1945, **67**, 351.
[16] De More, Wilcox, and Goldstein, *J. Chem. Phys.*, 1954, **22**, 876.

Alternatively, our estimates of $\mu_{soln.}$ may be too high. It is seen from Table 5 that the $_{\infty}(P_2)$'s now presented are greater than those of previous authors: this could in part be due to the method of extrapolation used[17] which often leads to higher figures at infinite dilution

TABLE 6. *Predicted values of the ratio* $\mu_{soln.}/\mu_{gas}$.

Solute	Pyridine			Quinoline			*iso*Quinoline		
A }	6·1			6·1			7·7		
B } Geom. factors ...	6·2			8·7			7·3		
C }	2·9			2·9			2·9		
$(n_s)_D^{25}$	1·5074			1·6247			1·6229		
Solvent	l.p.	CCl_4	C_6H_6	l.p.	CCl_4	C_6H_6	l.p.	CCl_4	C_6H_6
μ_s/μ_g [10a]	0·954	0·928	0·918	0·995	0·982	0·975	0·963	0·943	0·934
μ_s/μ_g [13]	0·952	0·918	0·912	0·994	0·966	0·961	0·944	0·908	0·903
μ_s/μ_g [10c]	0·962	0·934	0·920	0·979	0·969	0·964	0·984	0·968	0·956
μ_s/μ_g (Exptl.)	1·02	1·06	1·01	0·95	0·99	0·98	0·95	0·97	0·96
	±0·03	±0·03	±0·03	±0·06	±0·06	±0·06	±0·04	±0·04	±0·04

For the above, where necessary, the following properties of the solvents at 25° have been used:

Solvent	d_4^{25}	$(n_s^2)_D$	ε_1	$(\varepsilon_1 - 1)/(\varepsilon_1 + 2)$
Light petroleum	0·6959	1·9182	1·9300	0·2366
Carbon tetrachloride	1·58454	2·1243	2·2270	0·2903
Benzene	0·87378	2·2419	2·2725	0·2978

than does the older (and less certain) graphical procedure; in this connection it is relevant that the actual experimental observations by Le Fèvre and Smith are, at their concentrations, concordant with those now found.

Real exaltations of *apparent* moments in solution could arise from at least two causes: association of solute and solvent giving a polar complex, or solute–solvent interactions causing the atomic polarisation of the dissolved molecule to be greater than that of the gaseous molecule. Partington and Middleton[18] reported, without practical details, the moments of pyridine in carbon tetrachloride and benzene as 2·33 and 2·26 D, respectively; in other media results were lower (cf. Table 5) and the suggestion was made that pyridine forms an adduct with carbon tetrachloride; evidence was cited that this substance undergoes some kind of association with benzene and toluene (in which the apparent moment was given as 2·26 D); however, the fact (Table 6) that $\mu_{soln.}/\mu_{gas}$ (exptl.) is 1·02 in light petroleum, 1·06 in carbon tetrachloride, and 1·01 in benzene does not offer much support for a hypothesis that a polar complex C_5H_5N,CCl_4 is formed. Nevertheless solvation in general might alter the force constants for the various bending modes of the dissolved molecule (stretching frequencies seem to be reduced by solvents, cf. Bayliss, Cole, and Little[19]) and thus (cf. Le Fèvre and Rao[20]) affect the atomic contribution $_AP$ to the distortion polarisation $_DP$. The literature contains much evidence[21] which suggests that atom polarisations of polar species may sometimes be unexpectedly greater in solutions than in gases. In the particular case of pyridine, $_DP_{pyridine} = 24{\cdot}1$ c.c. is likely to be an underestimate: since pyridine possesses two polar links (C–N) and benzene none, $_AP_{pyridine}$ should exceed $_AP_{benzene}$, which[20] is *ca.* 1 c.c. From Goethals's finding[22] that P minus R for 4 : 4′-dipyridyl is 6·9 ± 2·0 c.c., a reasonable value for $_AP_{pyridine}$ might well lie between 3·5 and 4·5 c.c. if this is added to R_∞ (23·3 c.c. calculated from refractivities given in Landolt–Börnstein's "Tabellen," 1912 edn.), then $_DP$ becomes 26·8—27·8 c.c.

This is not far from the value $1{\cdot}1R_D = 26{\cdot}5$ c.c. assumed by Leis and Curran.[23] Further, from the temperature dependence of the polarisations of solutions of pyridine in benzene, Rau and Narayanaswamy[24] calculated an A term of 31·3 ± 1·2 c.c. Use of this figure, in

[17] Cf. Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1.
[18] Partington and Middleton, *Nature*, 1938, **141**, 516.
[19] Bayliss, Cole, and Little, *Austral. J. Chem.*, 1955, **8**, 26.
[20] Le Fèvre and Rao, *Austral. J. Chem.*, 1954, **7**, 135; 1955, **8**, 39.
[21] *E.g.*, Smythe and Walls, *J. Amer. Chem. Soc.*, 1930, **52**, 2234; Morgan and Lowry, *J. Phys. Chem.*, 1930, **34**, 2385; Jenkins, *Trans. Faraday Soc.*, 1934, **30**, 739; Sugden, *ibid.*, p. 734.
[22] Goethals, *Rec. Trav. chim.*, 1935, **54**, 299.
[23] Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79.
[24] Rau and Naraswamy, *Z. phys. Chem.*, 1934, *B*, **26**, 23.

conjunction with ${}_{\infty}P_2 = 127{\cdot}8$ c.c. (Table 5), leads to moments of $2{\cdot}17 \pm 0{\cdot}01$ D, which do not exceed $\mu_{gas} = 2{\cdot}19$ D obtained *via* the refractivity method (with $R_D = 24{\cdot}1$ c.c.) or $\mu_{gas} = 2{\cdot}23$ D, *via* the vapour polarisation–temperature relation (see Table 2). It is relevant that Rau and Narayanaswamy found that the A terms for quinoline–benzene and *iso*quinoline–benzene systems were much closer to R_D than was that for pyridine.

We conclude, therefore, that the apparent alterations of polarity by solution of these bases, particularly of pyridine, may be due to causes other than the physical solvent effects for which the equations used in Table 6 were devised.

Finally, we have considered the moments deducible from the ϵ_{25} and d_4^{25} of the same heterocycles in the liquid state.[25] These are set out in Table 7; the dielectric constants

TABLE 7. *Calculations of μ_{gas} from data on the pure liquids.*

	ϵ_{25}	d_4^{25}	$_{\infty}P_{liquid}$ (c.c.)	μ_{liquid}	μ_{gas} (Onsager)	μ_{gas} (Buckingham and Le Fèvre)	μ_{gas} (exptl.)
Pyridine	12·01	0·978	63·5	1·39	2·1	2·5	2·2
Quinoline	8·704	1·090	85·3	1·46	1·9	2·1	2·3
*iso*Quinoline	10·71	1·099	89·8	1·54	2·2	2·7	2·7

are close to those given in the "Table of Dielectric Constants of Pure Liquids."[26] Refractive indexes and shape factors are from Table 6. Under μ_{liquid} are the apparent moments computed from the differences between the total polarisations, $(\epsilon - 1)M/(\epsilon + 2)d$, and the molecular refractions of the liquids. The values of μ_{gas} calculated by Onsager's equation[27] are compared with those derived from μ_{liquid} by use of Buckingham and Le Fèvre's empirical relation (5).[10c] The results favour the latter expression in two cases.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, September 6th*, 1955.]

[25] Le Fèvre, *J.*, 1935, 773.
[26] Nat. Bur. Stands. Circular 514, Washington, 1951.
[27] Onsager, *J. Amer. Chem. Soc.*, 1936, **58**, 1486.

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287. *Stereochemistry of Tropane Alkaloids. Part IX.* Selective Quaternisation of Tropan-3α-ol and Tropan-3β-ol and of their Derivatives.*

By GÁBOR FODOR, KÁROLY KOCZKA, and JÁNOS LESTYÁN.

"Direct" and "reverse" quaternisation of tropan-3β-ol and nortropan-3β-ol has given *N*-epimeric *N*-ethoxycarbonylmethyl- and *N*-carboxymethyl-tropanium salts to which definite configurations have been allotted. Tropan-3α-ol ethiodide and *N*-ethylnortropan-3α-ol methiodide have been shown to differ, as have the epimeric *N*-ethoxycarbonylmethyl-3α-hydroxytropanium iodides and the derived betaines.

THE formation of a particular *N*-epimer, depending upon the order of attachment of groups A and B (*e.g.*, methyl and ethoxycarbonylmethyl) to the nitrogen atom of nor-ψ-tropine,[1] nortropine,[2,3] (±)-tropane-3α : 6β-diol,[4] and norecgoninol [5] has already been

* Part VIII, Fodor, Kovács, and Halmos, *J.*, 1956, 873.

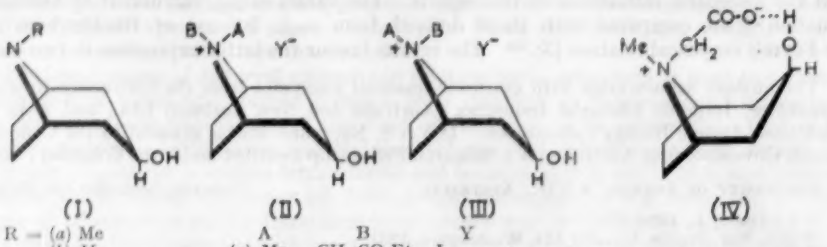
[1] Fodor, Meeting Hung. Chem. Soc., Sept. 19th, 1952; Fodor, Koczka, and Lestyán, *Magyar Kém. Folyóirat*, 1953, **59**, 242.
[2] Tóth, Lecture, Meeting Soc. Hung. Chemists, Debrecen, September 26th, 1953; Fodor, Tóth, Lestyán, and Vincze, *Vegyip. Kut. Int. Közl.*, 1953, **4**, 293.
[3] Cf. Findlay, *J. Amer. Chem. Soc.*, 1953, **75**, 3204.
[4] Part VI, Fodor, Tóth, and Vincze, *J.*, 1955, 3504.
[5] Fodor, XIVth Congress Int. Union Pure Appl. Chem., Zürich, July 21st, 1955; Kovács, Fodor, and Halmos, *J.*, 1956, 873.

discussed.[6] "Direct" and "reverse" quaternisations of nortropane-3β- and -3α-ol * are now reported.

With ethyl iodoacetate tropan-3β-ol (I*a*) gave *N*-ethoxycarbonylmethyl-3β-hydroxytropanium iodide (II*a*). *N*-Ethoxycarbonylmethylnortropan-3β-ol (I*c*) [from nortropane-3β-ol (I*b*) and ethyl *O*-toluene-*p*-sulphonylglycollate] gave, with methyl iodide, the *N*-epimer (III*a*) of (II*a*). The bromides were similarly prepared. The diastereoisomers, formed from the tertiary bases under identical conditions, showed different m. p.s, solubilities, and crystal forms.

The betaine (IV), obtained by hydrolysis of the ester (III*a*), readily lost a molecule of water of crystallisation, but the betaine hydrate (V) formed from the epimeric ester (II*a*) was not dehydrated even after 2 hr. at 110°/30 mm. This highly stereospecific behaviour may be explained by assuming hydrogen bonding between water and carboxylate anion, pointing to the configuration (V) for the betaine hydrate. The stability of the anhydrous form of the epimeric betaine might be due to hydrogen bonding between carboxylate anion and the 3-hydroxyl group as permitted by the configuration (IV). The two betaine picrates showed different solubilities and crystal forms.

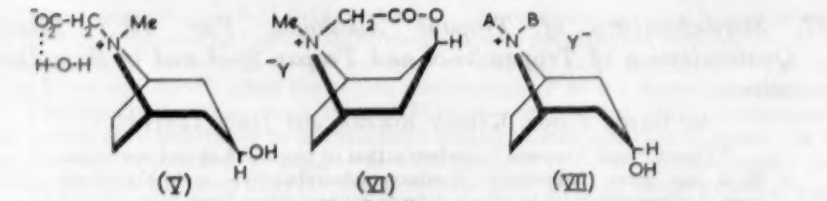
With hydrogen bromide and iodide the betaines gave *N*-epimeric carboxymethyl derivatives (II*b*) and (III*b*). The reconversion of the bromide (II*b*) into the *N*-ethoxycarbonylmethyl-3β-hydroxytropanium bromide (II*a*) by diazoethane is evidence for the absence of stereomutation during these changes.



(I) (II) (III) (IV)

R = (*a*) Me, (*b*) H, (*c*) $CH_2{\cdot}CO_2Et$

	A	B	Y
(*a*)	Me	$CH_2{\cdot}CO_2Et$	I
(*b*)	Me	$CH_2{\cdot}CO_2H$	I, Br, Cl } or picrate



(V) (VI) (VII)

Y = I or Br

	A	B	Y	
(*a*)	Me	Et	I	or picrate
(*b*)	Et	Me	I	or picrate
(*c*)	Me	$CH_2{\cdot}CO_2Et$	I	or picrate
(*d*)	$CH_2{\cdot}CO_2Et$	Me	I	or picrate

Unfortunately, although the epimeric carboxylic acids behaved differently towards lactonising reagents, quantitative cyclisation could not be achieved. Even concentrated sulphuric acid at 0° left the acid from tropan-3β-ol intact. Evaporation of the betaine (IV) with hydrobromic and hydriodic acid caused partial cyclisation, and although separation of the lactone (VI) and of the acid (III*b*) proved difficult, infra-red † maxima characteristic

* For nomenclature see *J.*, 1953, 721 and 1955, 3504.

† We are indebted to Dr. Pliva (Institute for Organic Chemical Research, Czechoslovakian Academy of Science, Prague) for these spectra.

[6] Fodor, *Acta Chim. Acad. Sci. Hung.*, 1955, **5**, 379; *Experientia*, 1955, **11**, 129; Meeting, Chem. Soc. DDR, Leipzig, October 23rd, 1954; *Angew. Chem.*, 1955, **67**, 211.

of lactones (at 1750 and 1623 cm.$^{-1}$) were detected in a selected crop of crystals. With acetic anhydride the acid chloride gave only the acetate of a mixed anhydride. Although pyrolysis of *N*-ethoxycarbonylmethyl-3β-hydroxynortropanium toluene-*p*-sulphonate gave

*X-Ray diffraction patterns.**

N-Ethoxycarbonylmethyl-3α-hydroxytropanium iodide (VII*c* or *d*)		*N*-Ethoxycarbonylmethylnortropine methiodide (VII*b* or *a*)		*Na*-(?)Carboxymethyl-3α-hydroxytropanium betaine		*Nb*-(?)Carboxymethyl-3α-hydroxytropanium betaine		*N*-Ethylnortropine methiodide (VII*a* or *b*)		Tropine ethiodide (VII*b* or *a*)	
d	*r*	*d*	*r*	*d*	*r*	*d*	*r*	*d*	*r*	*d*	*r*
7·06	M	8·00	VW	6·84	VW	7·99	W	5·986	VW	6·058	VW
6·50	M	7·07	S	6·38	S	6·68	M	5·546	M	5·63	VW
5·63	VW	6·61	S	6·11	VW	6·08	M	5·250	S	5·233	VS
5·22	M	5·19	VS	5·68	W	5·57	VS	5·078	VW	3·919	VW
4·90	W	4·64	M	5·40	VW	5·11	S	4·641	M	3·731	S
4·69	W	4·45	M	5·26	VW	4·88	M	3·909	VW	3·334	VW
4·45	W	4·16	S	5·01	S	4·21	S	3·762	VS	3·191	S
4·24	S	3·88	W	4·76	VW	3·93	M	3·620	VW	3·069	M
4·11	S	3·61	S	4·67	W	3·48	M	3·441	VW	2·653	VW
3·92	W	3·51	S	4·59	VW	3·20	W	3·310	S	2·441	M
3·53	W	3·37	S	4·45	VW	2·95	VS	3·210	M	2·384	M
3·44	VS	3·30	S	4·34	NS	2·82	M	3·115	S	2·178	M
3·35	W	3·13	S	4·10	W	2·66	M	3·042	VW	2·057	M
3·15	S	2·95	VW	3·91	VW	2·58	W	2·812	M	1·891	VW
2·80	M	2·83	W	3·81	S	2·49	M	2·609	VW	1·806	M
2·53	M	2·70	W	3·65	VW	2·37	W	2·454	M	1·783	M
2·43	M	2·59	VW	3·38	S	2·31	VW	2·344	VW	1·797	VW
2·35	W	2·52	VW	3·34	VW	2·24	W	2·257	VW	1·623	VW
2·30	W	2·46	VW	3·24	W	2·16	M	2·223	VW		
2·25	W	2·39	M	2·97	M	2·10	M	2·129	M		
2·19	VW	2·28	S	2·89	S	1·988	W	2·018	VW		
2·14	VW	2·13	W	2·73	W	1·933	VW	1·986	VW		
2·07	M	2·07	W	2·66	VW	1·899	VW	1·959	VW		
2·000	M	1·991	M	2·52	W	1·842	M	1·905	W		
1·900	M	1·905	W	2·43	M	1·789	VW	1·805	VW		
1·811	VW	1·871	VW	2·33	VW	1·724	VW	1·787	VW		
1·779	M	1·822	M	2·24	M	1·662	M	1·693	VW		
1·736	W	1·791	VW	2·15	M	1·594	VW	1·642	VW		
1·692	W	1·760	VW	2·13	VW	1·561	VW	1·612	VW		
1·644	VW	1·729	VW	2·03	W	1·487	W	1·569	VW		
1·605	W	1·660	W	1·952	W	1·433	VW	1·499	VW		
1·559	W	1·605	VW	1·812	M	1·398	VW	1·417	VW		
1·502	W	1·589	VW	1·741	W	1·331	VW	1·365	VW		
1·448	VW	1·555	W	1·655	W	1·272	VW	1·320	VW		
1·404	VW	1·507	W	1·563	VW	1·241	VW	1·294	VW		
1·367	VW	1·496	VW			1·225	VW				
1·326	VW	1·455	W			1·202	VW				
1·264	VW	1·423	W			1·122	VW				
1·221	VW	1·382	VW			1·101	VW				
1·154	VW	1·363	VW			1·070	VW				
1·101	VW	1·307	W								
1·058	VW	1·273	VW								
		1·222	VW								
		1·197	W								
		1·147	VW								
		1·123	VW								
		1·110	VW								
		1·101	VW								
		1·092	VW								
		1·069	VW								

* Cu-K_α radiation was employed with a nickel-foil filter.
d = Interplanar spacing (Å).
r = Relative line strength (visually determined).
VS = very strong; VW = very weak; S = strong; W = weak; M = medium.

only 3β-hydroxytropanium toluene-*p*-sulphonate (presumably by loss of ethylene followed by decarboxylation [7]), ethoxycarbonylmethyltropanium iodides were observed to resolidify above their m. p.s, forming a mixture from which were isolated tropan-3β-ol methiodide, the lactone (VI), and (probably) *NN*-di(ethoxycarbonylmethyl)-3β-hydroxynortropanium iodide. Thus stereomutation, intermolecular alkyl-cation exchange, and lactonisation of the intermediate *Na*-ethoxycarbonylmethyl compound occur.

[7] Cf. Jeffreys, *J.*, 1955, 2475.

Lactone formation by the *N*-epimer from "reverse" quaternisation permits the specification of the *N*-substituents as *Na*-methyl and *Na*-ethoxycarbonylmethyl in the compounds (I*a*) and (I*c*), in agreement with the predictions from conformational analysis [3,4,5] of the greater stability of an axial 2-substituent in 1 : 3-diaxially substituted *cyclo*hexanes.

The difficulty of lactone formation from ψ-nortropine, as contrasted with the cases of oscine and tropane-3α : 6β-diol, may be due to the prevalence of the chair-form in tropan-3β-ol derivatives.[9,6] The formation of a lactone-salt,[10] involving the primary hydroxyl group, by the action of methyl iodide upon *N*-ethoxycarbonylmethylnorecgoninol diacetate agrees with this assumption, since in this case lactonisation can occur even with the ring in chair-form.

Some experiments with tropan-3α-ol have also been done. With ethyl iodoacetate it gave an *N*-epimer (VII*c* or *d*) different from that (VII*d* or *c*) obtained by ethoxycarbonylmethylation and methylation of nortropan-3α-ol. In addition to crystal photographs, *X*-ray examination [11] (see below) proved these epimers different. The related betaines were also prepared.

Whilst this work was in progress Findlay [3] claimed that, although *N*-ethylnortropine propiodide differed from *N*-propylnortropine ethiodide, the salts from tropine and ethyl iodide and from *N*-ethylnortropine and methyl iodide were the same. This last finding was not consistent with our observations [1,4,5] on the ethoxycarbonylmethyl derivatives and we therefore examined the methylation of *N*-ethylnortropine and the ethylation of tropine. Professor S. Koch and Dr. Gy. Grasselly of the Institute of Mineralogy, Szeged University, found the resulting tropine ethiodide to form optically isotropic crystals whilst the *N*-ethylnortropine crystal was anisotropic. The picrates were even more strikingly different. Thus, with these tropine bases also the order of quaternisation determines the *N*-configuration. Unfortunately, apart from *X*-ray examination (being undertaken by C. H. McGillavry, Amsterdam), methods are not available for determining the configuration of these compounds with α-hydroxyl groups, and at present particular orientations (VII*a* or *b*, *c* or *d*) can only be assigned by analogy with tropan-3β-ol and ecgoninol derivatives.

Findlay's interpretation of his findings cannot be maintained. Our observations and ideas have recently been corroborated by Zeile and Schulz [12] from infrared examination of a series of *N*-epimeric tropan-3α- and -3β-ols.

Experimental

Ethyl Toluene-p-*sulphonylglycollate*.—Ethyl diazoacetate (7·35 g.) in ethyl acetate (50 ml.) was added drop by drop, with shaking, to toluene-*p*-sulphonic acid (11 g.) in the same solvent (50 ml.). After 2 hr. gas evolution had stopped and the solvent was evaporated *in vacuo*. The residue was washed with water (500 ml.) and dissolved in ether. Removal of the latter and crystallisation from alcohol gave the *ester* (5 g.), m. p. 50—52° (Found : C, 51·3; H, 5·3; S, 12·45. $C_{11}H_{14}O_5S$ requires C, 51·15; H, 5·45; S, 12·4%).

N-*Ethoxycarbonylmethylnortropan*-3β-*ol* (I*c*).—Nortropan-3β-ol (1·27 g.), ethyl *O*-toluene-*p*-sulphonylglycollate (7·58 g.), and dry ethanol (20 ml.) were refluxed for 4 hr. Removal of the solvent and trituration with ether gave N-*ethoxycarbonylmethyl*-3β-*hydroxynortropanium toluene*-p-*sulphonate*, m. p. 121—123° (Found : C, 56·3; H, 7·6; N, 3·4. $C_{18}H_{27}O_6NS$ requires C, 56·0; H, 7·0; N, 3·6%), as an oil which slowly crystallised.

Na-*Ethoxycarbonylmethyl*-3β-*hydroxytropanium Iodide* (III*a*).—The above salt (5·15 g.) in dry ethanol (20 ml.) was treated in turn with 1·28N-sodium ethoxide (10·4 ml.) and dry benzene (50 ml.). Sodium toluene-*p*-sulphonate (2·32 g.) was removed and the filtrate and methyl iodide (4·56 g.) were kept in a stoppered flask (100 ml.) at 20° for 20 hr. The crystals [3·085 g.; m. p.

[8] Barton, *Chem. and Ind.*, 1953, 664.

[9] Jones, *J. Amer. Chem. Soc.*, 1953, **75**, 4839; Archer and Lewis, *Chem. and Ind.*, 1954, 833; Wisser, Manassen, and de Vries, *Acta Cryst.*, 1954, **7**, 288; Nickon, *J. Amer. Chem. Soc.*, 1955, **77**, 4094.

[10] Kovács, Fodor, and Halmos, Part VIII, *J.*, 1956, 873.

[11] For these measurements we are grateful to Dr. A. Almásy, Research Institute for Heavy Chemical Industry, Veszprém, and to Dr. Gy. Bácskay, Head of the same Department.

[12] *Chem. Ber.*, 1955, **88**, 1078.

209° (decomp.)] (Found : C, 40·2; H, 6·5; N, 4·0; I^-, 35·3. $C_{12}H_{22}O_2NI$ requires C, 40·6; H, 6·2; N, 4·0; I^-, 35·7%) were collected and washed with benzene (12 ml.) and ethanol (3 ml.). Evaporation of the mother-liquor gave a wet crystalline powder (1·41 g.) which was collected with the help of dry acetone, giving a second crop (0·695 g.) of *iodide*, m. p. 206°, identical with the first.

Nb-*Ethoxycarbonylmethyl*-3β-*hydroxytropanium Bromide* (IIa).—(*a*) Tropan-3β-ol (2·82 g.), ethyl bromoacetate (3·34 g.), and benzene (20 ml.) were kept at 25° for 24 hr. The product (5·75 g.) gave prisms of the ***bromide*** (3·08 g.), m. p. 214° (Found : Br^-, 25·1. $C_{12}H_{22}O_3NBr$ requires Br^-, 26%), on crystallisation from ethanol.

(*b*) The salt (IIb) (0·5 g. ; see below) in alcohol (70 ml.) was treated with ethereal diazoethane (0·024 g./ml.), and when nitrogen evolution ceased more diazoethane solution (10 ml.) was added. After ½ hr. the solvent was removed and the product, m. p. 206—208° (alone and mixed with the above specimen), was collected with acetone.

Nb-*Ethoxycarbonylmethyl*-3β-*hydroxytropanium Iodide* (IIa).—Tropan-3β-ol (2·15 g.), dry ethanol (30 ml.), benzene (50 ml.), and ethyl iodoacetate (3·9 g.) were kept for 17 hr. ; a first crop of crystals [4·23 g. ; m. p. 204° (decomp.) (Found : C, 40·5; H, 6·4; N, 4·2; I^-, 35·8. $C_{12}H_{22}O_3NI$ requires C, 40·5; H, 6·2; N, 4·0; I^-, 35·7%)] was collected. Evaporation of the mother-liquor and trituration with acetone gave a second crop (0·81 g.), m. p. 199—201°.

10 Ml. of dry ethanol dissolved 1·4 g. of the salt (IIIa) and 0·31 g. of the epimer (IIa).

Betaines from the Ester Salts.—An aqueous solution of the salt (IIb) or (IIIa) (2·2 g.) was shaken with silver oxide (2·2 g.) for ½ hr. Filtration, evaporation, and recrystallisation, from ethanol (10 ml.), of the product from (IIa) gave the *betaine* (V) (0·3 g.), m. p. 270° (Found : C, 55·25; H, 8·9; N, 6·7. $C_{10}H_{17}O_3N,H_2O$ requires C, 55·2; H, 8·75; N, 6·4%) after drying at 110°/30 mm. for 2 hr. A second crop (0·7 g.) separated later. Evaporation of a solution of the betaine (V) (5·6 g.) in constant-boiling hydriodic acid, and crystallisation of the residue from ethanol, gave the *iodide* (IIb) (6·7 g.), m. p. 214° (Found : C, 36·2; H, 6·0; N, 4·5; I^-, 37·4. $C_{10}H_{18}O_3NI$ requires C, 36·7; H, 5·5; N, 4·3; I^-, 38·8%). The betaine (V) (0·22 g.) with picric acid (0·23 g.) in ethanol (10 ml.) gave, after 24 hr. at 0°, yellow needles of the *picrate*, m. p. 188° (Found : C, 45·2; H, 5·2. $C_{16}H_{20}O_{10}N_4$ requires C, 44·9; H, 4·7%). In the way described below the betaine (V) gave the *chloride* (IIb), m. p. 252° (Found : Cl^-, 15·1. $C_{10}H_{18}O_3NCl$ requires Cl^-, 15·05%).

The *betaine* (IV), m. p. >300° (Found : C, 60·4; H, 8·7; N, 7·0. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·5; N, 7·0%) (after drying as above), from the salt (IIIa) crystallised from ethanol–ether. This betaine (0·20 g.) with picric acid (0·3 g.) and ethanol (10 ml.) gave crystals (0·15 g.) after 1 day at 0°, and ether precipitated a second crop (0·1804 g.). The pure *picrate*, m. p. 168° (Found : C, 45·3; H, 5·0; N, 12·9, 13·3. $C_{16}H_{20}O_{10}N_4$ requires C, 44·9; H, 4·7; N, 13·1%), crystallised from ethanol. The betaine (IV) (0·140 g.) in dry ethanol (20 ml.) gave with 5N-hydrogen chloride in ethanol (1·2 ml.) crystals of Na-*carboxymethyl*-3β-*hydroxytropanium chloride* (IIIb), m. p. 220° (decomp.) (Found : Cl^-, 14·9%).

Hydrazide of Nb-*Carboxymethyl*-3β-*hydroxytropanium Iodide*.—The iodide (IIa) (1·775 g.), hydrazine hydrate (2 ml.), and ethanol (65 ml.) were refluxed for 2 hr. Set aside overnight, the solution deposited needles (1·10 g.) which from ethanol gave the *hydrazide*, m. p. 209—211° (Found : C, 35·5; H, 6·1; N, 12·1; I^-, 36·65. $C_{10}H_{20}O_2N_3I$ requires C, 35·15; H, 5·95; N, 12·3; I^-, 37·1%).

In the same way the epimer (IIIa) (0·43 g.), hydrazine hydrate (0·5 ml.), and ethanol (15 ml.) gave the *N-epimeric hydrazide* as plates, m. p. 191° (Found : C, 35·1; H, 6·1; N, 12·2; I^-, 35·95, 36·2%). The mixed m. p. was 180—182°.

Lactone of Na-*Carboxymethyl*-3β-*hydroxytropanium Iodide*.—(*a*) The solution of the acid methiodide (IIIb) (1·05 g.) in fuming hydriodic acid (10 ml.) was evaporated to dryness under reduced pressure. The residue was crystallised repeatedly from ethanol–ether, the iodide-ion content of each fraction being checked. Unchanged starting material occurred in the first three crops, while the *lactone iodide* (VI), m. p. 281° (decomp.) (Found : C, 39·1; H, 5·9; I^-, 41·85. OEt, 0. $C_{10}H_{14}O_2NCl$ requires C, 38·8; H, 5·2; I^-, 41·1%), was obtained from crops (4) and (5). The infrared spectrum showed bands at 1750 and 1625 $cm.^{-1}$.

(*b*) *Nb*-Ethoxycarbonylmethyl-3β-hydroxytropanium iodide (IIa) (12·6 g.) in a glass tube was placed directly into an oil-bath at 230°. Melting was complete in 7 min. and the melt resolidified (the loss in weight was 1·89 g.). It was extracted with water (130 ml.), leaving some solid undissolved (0·39 g.). The solution was shaken for 2 hr. with charcoal, filtered, and then concentrated *in vacuo*, giving a total of 9·07 g. of crystals. The portion (4·80 g.) of these left undissolved by boiling acetone (74 ml.) consisted mainly of tropan-3β-ol methiodide, obtained

pure (Found : I^-, 44·75. Calc. for $C_9H_{16}ONI$: I^-, 44·8%) by crystallisation from methanol. The acetone extract gave, on cooling, the lactone (0·5 g.), m. p. 281° (decomp.) (Found : I^-, 41·8, 41·9%). [Recrystallisation from dimethylformamide and methanol–ether gave a specimen, m. p. 276° (decomp.) (Found : C, 38·5; H, 6·2; N, 4·7, 4·8; I^-, 41·3, 41·3%).] Two further crops appeared to consist mainly of the *di*-(N-*ethoxycarbonylmethyl*) *compound* (Found : I^-, 29·0. $C_{15}H_{26}O_5NI$ requires I^-, 29·7%). The salt (III*a*) gave essentially the same products on heating.

Pyrolysis of N-*Ethoxycarbonylmethyl*-3β-*hydroxynortropanium Toluene*-p-*sulphonate.*—The salt of (I*c*) (0·7 g.; m. p. 123°) was placed in an oil-bath, preheated to 185°, for 15 min. Trituration with acetone (3 ml.), filtration, and washing with acetone (6 ml.) gave a product (m. p. 168—173°) which on recrystallisation from acetone gave white crystals, m. p. 172—173° (Found : C, 57·25; H, 7·3; N, 4·8; S, 10·2. $C_{15}H_{23}O_4NS$ requires C, 57·5; H, 7·4; N, 4·5; S, 10·2%) alone and mixed with authentic 3-β-*hydroxytropanium toluene*-p-*sulphonate*.

Acid Chlorides.—(*a*) Betaine (IV) (0·2 g.) and thionyl chloride (1 ml.) were kept for 12 hr. at 20° and the mixture was then evaporated under reduced pressure. Kept in a desiccator, the oily residue crystallised, and when collected with acetone provided the hygroscopic *acid chloride*, m. p. 220° (decomp.) (Found : C, 46·8; H, 6·8; N, 5·65; Cl, 26·2. $C_{10}H_{17}O_2NCl_2$ requires C, 47·2; H, 6·7; N, 5·5; Cl, 27·9%), which did not react with pyridine during 10 min. on the steam-bath.

(*b*) The betaine (V) gave a sensitive acid chloride which did not react with pyridine.

Mixed Anhydride of Acetic Acid and Na-*Carboxymethyl*-3β *acetoxytropanium Picrate.*—Betaine (IV) (0·1 g.) and acetic anhydride (1 ml.) were heated 2 hr. on the steam-bath. Evaporation of the solution *in vacuo* and treatment of the oil [in acetone (5 ml.)] with picric acid (0·2 g.) in ether (2 ml.) gave the *picrate*, m. p. 165—167° (Found : C, 47·05; H, 5·2; N, 10·7. $C_{20}H_{24}O_{12}N_4$ requires C, 46·9; H, 4·7; N, 10·9%).

N-*Ethoxycarbonylmethyl*-3α-*hydroxytropanium Iodide* (VII*c or d*).—Tropine (2·19 g.) [obtained (11·3 g.; m. p. 59—61°) by hydrogenating tropinone (13·5 g.) in ethanol (120 ml.) over Raney nickel [13] at 60—70°/85—100 atm. for 8 hr.], dry ethanol (20 ml.), benzene (20 ml.), and ethyl iodoacetate (3·5 g.) were kept at 20° for 9 hr. Recrystallisation of the product from ethanol gave the *salt* (0·48 g.), m. p. 210° (Found : I^-, 35·7. $C_{12}H_{22}O_2NI$ requires I^-, 35·7%). A second crop (1·2 g.) was obtained from the mother-liquor.

N-*Ethoxycarbonylmethyl*-3α-*hydroxynortropanium Toluene*-p-*sulphonate.*—Nortropine (3·2 g). (obtained best by von Braun degradation of tropine [14]), ethyl *O*-toluene-*p*-sulphonylglycollate (6·48 g.), and ethanol (50 ml.) were refluxed for 8 hr. Evaporation gave an oil which crystallised (8·1 g.) when triturated with dry ether. The *toluene*-p-*sulphonate*, m. p. 152° (Found : C, 56·2; H, 6·8; N, 3·8; S, 8·0. $C_{18}H_{27}O_6NS$ requires C, 56·1; H, 7·1; N, 3·6; S, 8·3%), crystallised from acetone. When carried out in acetone the reaction gave a 52% yield.

N-*Ethoxycarbonylmethyl*-3α-*hydroxytropanium Iodide* (VII*d or c*).—To the toluene-*p*-sulphonate (5·95 g.) in dry ethanol (20 ml.) 1·24N-sodium ethoxide (12·5 ml.) was added. Sodium toluene-*p*-sulphonate was removed and the filtrate was treated with benzene (10 ml.) and methyl iodide (6·8 g.). After 9 hr. at 25° the *iodide* (0·86 g.), m. p. 215° (Found : I^-, 35·8%), was collected. Cooling gave a second crop (3·95 g.), m. p. 214°. Photomicrographs and *X*-ray examination (see Table) proved it different from the *N*-epimer described above.

N-*Epimeric Betaines.*—(*a*) The ester iodide (VII*c* or *d*) (4·2 g.), water (40 ml.) and silver oxide (5·4 g.) were shaken for 1 hr. Filtration, evaporation *in vacuo*, and crystallisation of the residue from ethanol–ether gave the *betaine dihydrate* (transformation temp. 90°), m. p. 284° (Found : C, 51·05; H, 9·2; N, 5·9. $C_{10}H_{17}O_2N,2H_2O$ requires C, 51·05; H, 9·0; N, 5·95%). Drying over phosphoric anhydride (111°/10 mm., 2 hr.) gave the *monohydrate* (Found : C, 55·4; H, 9·8. $C_{10}H_{17}O_2N,H_2O$ requires C, 55·3; H, 9·7%), and with boiling xylene (10 mm., 2 hr.) the *anhydrous betaine* (Found : C, 60·7; H, 9·05. $C_{10}H_{17}O_2N$ requires C, 60·3; H, 8·6%). The dehydration was reversible.

(*b*) The ester iodide (VII*d* or *c*) (3 g.) gave in the same way the betaine (1·47 g.), m. p. 278°. Drying with boiling toluene (111°/10 mm., 1 hr.) gave the *monohydrate* (Found : C, 55·3; H, 8·8; N, 6·4%), and with xylene (140°/10 mm., 5 hr.) the *anhydrous betaine* (Found : C, 60·4; H, 8·8%). Treatment with water and recrystallisation gave the monohydrate again. *X*-Ray examination proved the anhydrous betaines different.

N-*Ethylnortropan*-3α-*ol.*—Nortropine (3·95 g.) and ethyl toluene-*p*-sulphonate (6·43 g.) were

[13] Cf. Keagle and Hartung, *J. Amer. Chem. Soc.*, 1946, **68**, 1608.
[14] Nickon and Fieser, *ibid.*, 1952, **74**, 5566.

refluxed in dry acetone (40 ml.) for 4 hr. Trituration of the residue with ether gave the salt (6·65 g., m. p. 121—134°). Recrystallisation from acetone gave the *toluene*-p-*sulphonate* (3·95 g.), m. p. 149—150° (Found: C, 58·95; H, 7·8; N, 4·4. $C_{16}H_{25}O_4NS$ requires C, 58·7; H, 7·7; N, 4·3%).

N-Ethylnortropan-3α-ol Methiodide (VII*a or b*).—The above salt (3·27 g.) in dry ethanol (10 ml.) and benzene (30 ml.) was treated with 1·87N-sodium ethoxide (5·35 ml.). Sodium toluene-*p*-sulphonate was removed and the filtrate was kept with methyl iodide (7·1 g.) for 20 hr. at room temperature. The crystals (1·7129 g.) and a second crop (0·7331 g.) had m. p. >300° (Found: C, 40·3; H, 7·1; N, 4·5; I^-, 42·85. Calc. for $C_{10}H_{20}ONI$: C, 40·4; H, 6·8; N, 4·7; I^-, 42·7%). Findlay [3] gave m. p. 316°. The *picrate*, m. p. 252—253° (Found: C, 48·2; H, 5·5; N, 13·9. $C_{16}H_{22}O_8N_4$ requires C, 48·2; H, 5·6; N, 14·1%), formed needles from ethanol.

Tropan-3α-ol Ethiodide (VII*b or a*).—Simultaneously with, and under the same conditions as, the above experiment, tropan-3α-ol (1·41 g.) and ethyl iodide (7·8 g.) were allowed to react in ethanol (10 ml.) and benzene (30 ml.). Cubic crystals (0·92 g.) and a second crop (0·3 g.), m. p. >300° (Found: C, 40·3; H, 6·9; N, 4·7; I^-, 42·6%), were obtained. Findlay [3] gave m. p. 316°. The *picrate*, m. p. 233—234° (Found: C, 48·4; H, 5·4; N, 14·1%), gave a marked (30°) mixed m. p. depression with the *N*-epimer described above.

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288. *Mesomorphism and Chemical Constitution. Part VII.* The Effect of Halogen Substitution on the Mesomorphism of the* trans-p-n-*Alkoxycinnamic Acids.*

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The preparation and mesomorphic characteristics of certain *trans*-4-*n*-alkoxy-3-halogenocinnamic acids are described. The breadth and polarisation of the *trans*-*p*-*n*-alkoxycinnamic acids are increased by halogen substitution, and the effect of these changes is shown by the altered thermal stabilities of the mesophases. The presence of chlorine or bromine does not entirely eliminate the mesomorphic properties, although in the broader bromo-derivatives the long-chain dodecyl, hexadecyl, and octadecyl ethers alone exhibit mesophases, and these are monotropic. On the other hand all *trans*-4-*n*-alkoxy-3-iodocinnamic acids are non-mesomorphic. Such behaviour accords with that of the *trans*-4-*n*-alkoxy-3-halogenobenzoic acids.

THE changes in mesomorphic behaviour which accompany substitution in the 3-position of the *p*-*n*-alkoxybenzoic acids and in the 5-position of the 6-*n*-alkoxy-2-naphthoic acids have already been examined.[1,2] In order to make further comparisons possible, a study has been made of the effect of halogen substitution on the mesomorphism of the *trans*-*p*-*n*-alkoxycinnamic acids.[3] The m. p.s and mesomorphic transition temperatures (solid–smectic or –nematic, smectic–nematic, and smectic– or nematic–isotropic) of the 3-chloro-, 3-bromo-, and 3-iodo-derivatives are contained respectively in Tables 1, 2, and 3. In the chloro-series thirteen *n*-ethers (methyl—decyl, dodecyl, hexadecyl, and octadecyl) were prepared and examined, but since in the bromo-series mesomorphism does not occur until the dodecyl ether, and in the iodo-series no anisotropic phases are found, only a few of the lower ethers were prepared.

* Part VI, Gray, Hartley, Ibbotson, and Brynmor Jones, *J.*, 1955, 4359.

[1] Gray and Brynmor Jones, *J.*, 1954, 2556.
[2] *Idem*, *J.*, 1955, 236.
[3] *Idem*, *J.*, 1954, 1467.

In the chloro-series, the hexyl ether is the first to exhibit mesomorphism and both the smectic and the nematic phase are monotropic. The lower m. p.s of the heptyl and octyl ether make possible enantiotropic nematic phases, but the smectic phases remain monotropic. The increasing stability of the smectic phase in the nonyl, decyl, and dodecyl

TABLE 1. trans-4-n-*Alkoxy*-3-*chlorocinnamic acids.*

	Temp. of transition to				Temp. of transition to		
Alkyl	smectic	nematic	isotropic	Alkyl	smectic	nematic	isotropic
Methyl	—	—	251°	Octyl	(127°)	130·5°	140°
Ethyl	—	—	206	Nonyl	125·5	131	138
Propyl	—	—	183·5	Decyl	122	133	137
Butyl	—	—	170	Dodecyl	116	133·5	134
Pentyl	—	—	159·5	Hexadecyl	115·5	—	129
Hexyl	(< 140·5°)	(144°)	148	Octadecyl	118·5	—	126·5
Heptyl	(120)	136·5	140·5				

TABLE 2. trans-4-n-*Alkoxy*-3-*bromocinnamic acids.*

	Temp. of transition to			Temp. of transition to	
Alkyl	isotropic	Alkyl	smectic	nematic	isotropic
Methyl	250·5°	Nonyl	—	—	139·5°
Ethyl	214·5	Decyl	—	—	136·5
Hexyl	160·5	Dodecyl	(<127°)	(128°)	129
Heptyl	149	Hexadecyl	(122·5)	—	126
Octyl	142	Octadecyl	(121)	—	125

TABLE 3. trans-4-n-*Alkoxy*-3-*iodocinnamic acids.*

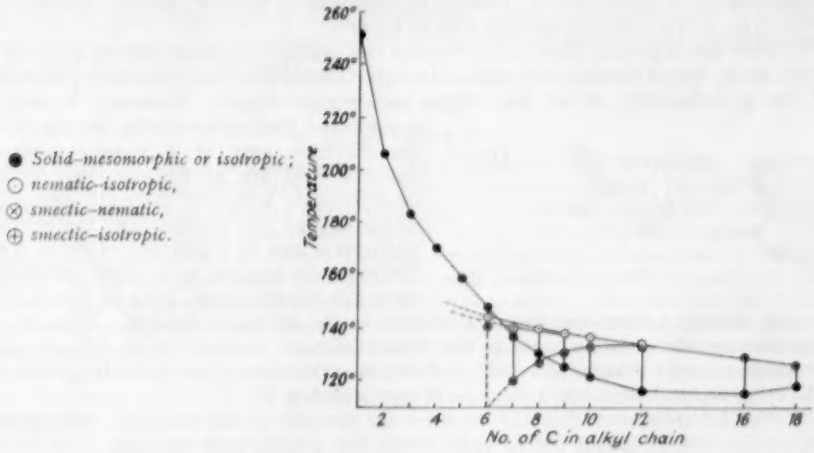
Alkyl	M. p.	Alkyl	M. p.	Alkyl	M. p.
Methyl	239·5°	Octyl	158°	Dodecyl	150·5°
Butyl	193	Nonyl	157·5	Hexadecyl	147·5
Hexyl	181	Decyl	156·5	Octadecyl	142
Heptyl	169				

ethers allows enantiotropic phases of both types. The hexadecyl and the octadecyl ether exhibit only smectic behaviour. When the m. p.s and mesomorphic transition temperatures for this series are plotted against the number of carbon atoms in the *n*-alkyl chain (see Figure), the points show the customary regularities found for homologous series of mesomorphic alkoxyarenecarboxylic acids. Thus, the smectic–nematic transition points for the heptyl—dodecyl ethers lie on a rising curve which reaches a maximum before joining the falling curve through the nematic- and smectic–isotropic points for the ethers containing even-carbon chains (hexyl—octadecyl). Only two ethers containing odd-carbon chains (heptyl and nonyl) give nematic–isotropic transition points, but these, as usual, lie slightly below the upper transition-point curve for even members of the series. These two points constitute what is probably the end of a similar smooth curve, which, if the isotropic melts of the lower ethers could supercool sufficiently, would pass through the " monotropic nematic–isotropic points " for the methyl, propyl, and pentyl ethers. The m. p. curve in this series is surprisingly regular and falls, steeply at first, to a minimum at the dodecyl ether, before rising to the m. p.s of the hexadecyl and the octadecyl ether. This curve, which is almost smooth, cuts the upper transition-point curve between hexyl and heptyl, and the smectic–nematic curve between octyl and nonyl, and so renders several of the phases monotropic. These are the figures in parentheses in Table 1. When the isotropic melt of the hexyl ether is cooled, the nematic phase first appears and the transition point is readily determined. Unless this phase is rapidly chilled, the smectic phase is not visible and crystallisation occurs at 140·5°. Consequently, the nematic–smectic transition point lies below this temperature, but it could not be determined. If, however, the smectic–nematic transition point curve (Figure) is extrapolated, the transition point for the hexyl ether is seen to be about 110°.

In the bromo-series, the dodecyl, hexadecyl, and octadecyl ethers alone exhibit mesophases. The isotropic melt of the dodecyl ether does not supercool greatly, and only the isotropic–nematic point could be determined. The hexadecyl and the octadecyl ether

show smectic phases, and in both cases these are monotropic. The upper transition points of these three ethers lie on a section of a curve, the whole of which would undoubtedly constitute a normal mesomorphic–isotropic transition-point curve if the lower members of the series were mesomorphic.

Mesomorphic–isotropic transition temperatures are available for the dodecyl, hexadecyl, and octadecyl ethers of the *p*-alkoxycinnamic acids,[3] and their 3-chloro- and 3-bromo-derivatives. The mean of the three values may be taken in each case as an indication of



the average relative mesomorphic stability for this particular part of the series. These are summarised in Table 4, which also includes the changes in average transition temperature on passing from the unsubstituted acid to the substituted acid.

TABLE 4.

3-Substituent in the *p*-alkoxycinnamic acid	H	Cl	Br
Average mesomorphic–isotropic transition temperature (C_{12}—C_{18})	160·5°	129·8°	123·8°
Decrease in transition temperature from unsubstituted acid		30·7°	36·7°

The introduction of the chlorine atom therefore decreases the mesomorphic transition temperature by 30·7°. This decrease in thermal stability must be the result of the two opposing effects of the chlorine substituent—first, the C–Cl dipole will increase the molecular polarisation and the mesomorphic thermal stability, and secondly, the increase in molecular breadth due to the chlorine atom will increase the molecular separation, weaken the intermolecular forces maintaining the molecular orientation in the mesophase, and decrease the thermal stability. The effect of bromine is only slightly greater than that of chlorine, and the decrease in average transition temperature from the unsubstituted acid is 36·7°—a result which accords with the fact that the C–Br dipole (1·71 μ) is not substantially different from the C–Cl dipole, and that the increase in breadth from chloro- to bromo-substituted cinnamic acid is only 0·27 Å. That is, the 6° thermal stability decrease from chloro- to bromo-series is the net result of these small changes in breadth and permanent polarisation, together with the different polarisability of the two molecule types.

Iodine as a substituent increases the molecular breadth more (1·83 Å), and the increase in permanent polarisation of the molecule (1·48 μ) is less than with chlorine and bromine. As a result, the 4-alkoxy-3-iodocinnamic acids show no mesomorphism.

The same general decrease in the mesomorphic thermal stability of the *p*-alkoxybenzoic acids has already been observed [1] when the molecular breadth is increased to such an extent that increased polarisation and polarisability fail to counteract the decrease in intermolecular cohesion. In this case the 4-alkoxy-3-fluoro- and 4-alkoxy-3-chlorobenzoic acids alone are mesomorphic. Considering once more the dodecyl—octadecyl

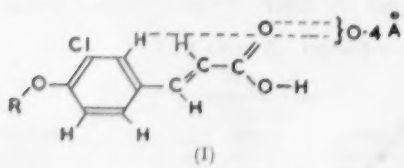
ethers, the average mesomorphic–isotropic transition temperatures, together with the corresponding decreases from unsubstituted to substituted acid, are given in Table 5.

TABLE 5.

3-Substituent in the 4-alkoxybenzoic acid	H	F	Cl
Average mesomorphic–isotropic transition temperature (C_{12}—C_{18})	133·5°	108·2°	84°
Decrease in transition temperature from unsubstituted acid		25·3°	49·5°

Here again an increase in substituent size decreases the mesomorphic stability, the fluorine atom (C–F dipole, 1·57 μ; breadth increase 0·43 Å) by 25·3°, and the chlorine atom (C–Cl dipole, 1·73 μ; breadth increase 1·18 Å) by 49·5°.

Chlorine has a greater effect in decreasing the average transition temperature of the benzoic acids than of the cinnamic acids, although it should alter the permanent polarisation and the polarisability of the two types to a similar degree. However, it must be remembered that, although the benzenoid and the ethylenic part of a *trans-p-n*-alkoxycinnamic acid are no broader than for a *p*-alkoxybenzoic acid, the carboxyl group protrudes beyond the benzene and the ethylenic hydrogen atoms to a distance of about 0·4 Å. The molecule appears to be most symmetrical when the alkoxy-group, lying in the plane of the ring, adopts a *trans*-configuration relative to the ethylenic linkage. Moreover, for steric reasons, the chlorine atom in the 3-position must be *trans* to the alkoxy-group. In consequence, the chlorine atom will probably lie on the side of the molecule on which the carboxyl group protrudes—an arrangement represented in (I).



(I)

A chlorine atom may therefore increase the breadth of the cinnamic acid molecule to a smaller extent (about 0·8 Å) than it will the benzoic acid molecule (1·18 Å), and consequently, its effect in reducing the mesomorphic thermal stability should be greater in the latter series. A similar result has been observed in the 6-alkoxy-5-chloro-2-naphthoic acids which are no broader than the unhalogenated acids.[2] In this case the chloro-derivatives have the higher mesomorphic transition temperatures. However, the 6-alkoxy-5-bromo-2-naphthoic acids, like the 4-alkoxy-3-bromo- and 4-alkoxy-3-chloro-cinnamic acids, are broader (0·22 Å) than the 5-chloro-acids. In both cases the bromine reduces the thermal stability compared with that of the chloro-derivatives, and it is interesting that the decreases (considering the C_{12}—C_{18} ethers in all cases) are very similar in each instance, 6° from chloro- to bromo-cinnamic acid, and 4·7° from chloro- to bromo-naphthoic acid.

No smectic–nematic transition temperatures are available for the 4-alkoxy-3-bromo-cinnamic acids, and, in considering the relative stability changes of the smectic phase, only the unsubstituted and 3-chloro-4-alkoxy-benzoic and -cinnamic acids need be considered. The average values for the nonyl, decyl, and dodecyl ethers are contained in Table 6.

TABLE 6.

3-Substituent	H	Cl	Decrease
Average smectic–nematic transition temperature (C_9—C_{12}) for:			
(*a*) *p*-alkoxybenzoic acids	122·7°	89·8°	32·9°
(*b*) *p*-alkoxycinnamic acids	150·5	132·5	18

Here again, chlorine decreases the mesomorphic thermal stability, but to a smaller extent in the cinnamic acids.

It is in general true that, relatively to the unsubstituted acid, any one substituent decreases the thermal stability of the smectic phase to a smaller extent than that of the nematic phase. This arises through the increases in polarisability and permanent polarisation of the acid dimer caused by, for example, the introduction of the chlorine atom. In the smectic phase, the component of the C–Cl dipole which acts at right angles to the long axis of the molecule reinforces that in neighbouring molecules. Together with the decrease in lateral cohesions arising from the increased molecular separation, this effect will lead to a less marked reduction in thermal stability of the smectic phase than of the nematic phase, in which this dipole reinforcement does not occur.

The order of decreasing mesomorphic thermal stability for unsubstituted alkoxyarenecarboxylic acids has already been given[3] as naphthoic > cinnamic > benzoic, and it is now seen that this sequence is also applicable to the substituted acids. The above order was originally related to the decreasing number of double bonds in the molecules, but is more accurately described in terms of the decreasing molecular polarisability as the number of C–H, C–C, and C=C bonds decreases. The marked stability of the phases of the 4′-*n*-alkoxydiphenyl-4-carboxylic acids, in which there are 12 carbon atoms and related bonds in the central nucleus, is a further illustration of this effect.[4]

The mesomorphic behaviour of these substituted cinnamic acids indicates that their configuration is *trans*. The *cis*-isomers would be considerably broader, and the molecular attractions would be much reduced.

Experimental

M. p.s are corrected.

Determination of Transition Temperatures.—The mesomorphic and polymorphic transition temperatures were determined in an electrically heated microscope block.[5] The enantiotropic mesomorphic changes were measured in the usual way, and all values, except those involving solid–mesomorphic transitions, were checked by both heating and cooling the specimen. Like the *trans-p-n*-alkoxycinnamic acids,[3] the 3-halogeno-derivatives tend to decompose on prolonged heating, so freshly mounted slides were used for each transition-point determination and exposure to high temperatures was minimised as far as possible. The procedure for determination of monotropic transition temperatures involving mesophases was as described for the 4-alkoxy-3-halogenobenzoic acids.[1] In these substituted cinnamic acids, the changes observed in polarised light were from the solid to the fine mosaic of smectic focal-conic groups, from the solid or the smectic phase to the mobile, threaded nematic phase (somewhat obscured by pseudomorphism in the 3-chloro-acids), and from the solid or the mesophase to the extinct isotropic liquid. In those members of both mesomorphic series which are purely smectic, characteristic bâtonnets are seen only when the isotropic liquid is cooled very slowly, and they very soon coalesce to give the fine mosaic of focal-conics.

Polymorphism occurs to a marked degree in the non-mesomorphic 4-alkoxy-3-iodocinnamic acids, and the solid–solid transition temperatures for this series are contained in the annexed table.

Alkyl	Transition temperature of Solid I–solid II	Alkyl	Transition temperature of Solid I–solid II	Solid II–solid III
Octyl	157·5°	Dodecyl	113°	—
Nonyl	141	Hexadecyl	62·5	116·5°
Decyl	132	Octadecyl	87·5	123

Preparation of Materials.—The *p-n*-alkoxybenzaldehydes were prepared by homologous alkylation (methyl—decyl, dodecyl, hexadecyl, and octadecyl) of *p*-hydroxybenzaldehyde as described by Gray and Brynmor Jones.[3]

4-n-*Alkoxy*-3-*chlorobenzaldehydes.* The *p-n*-alkoxybenzaldehyde (0·1 mole) was dissolved in glacial acetic acid (50 ml.), and to the solution was added dichloramine-T (12 g., 0·05 mole) in glacial acetic acid (25 ml.). After the addition of concentrated hydrochloric acid (0·1 ml.), the mixture was refluxed for 6 hr., cooled, diluted, and extracted with ether. The extract was washed with water, dilute aqueous sodium hydroxide, and again with water, and dried and the ether was removed. The residual, crude 4-n-*alkoxy*-3-*chlorobenzaldehydes* were distilled under reduced pressure and obtained as low-melting waxy solids. These products were very difficult to crystallise, and only one crystallisation from 90% ethanol was carried out. The solids give rather ill-defined m. p.s over a range of 2—4°, but give satisfactory results in the subsequent Knoevenagel condensation. The m. p.s and analyses are tabulated.

trans-4-n-*Alkoxy*-3-*chlorocinnamic acids.* The *p*-alkoxy-3-chlorobenzaldehyde (0·01 mole), malonic acid (1·6 g., 0·02 mole), pyridine (7 ml.), and piperidine (2 drops) were heated at 100° for 3 hr. The amount of pyridine was doubled in the case of the hexadecyloxy- and octadecyloxy-aldehyde. The precipitate obtained by pouring the mixture on ice (10 g.) and concentrated hydrochloric acid (10 ml.) was collected and washed with dilute hydrochloric acid and water. With the exception of the ethyl ether which was crystallised from benzene, the

[4] Gray, Hartley, and Brynmor Jones, *J.*, 1955, 1412.
[5] Gray, *Nature*, 1953, **172**, 1137.

4-Alkoxy-3-chlorobenzaldehydes.

Alkyl	B. p./mm.	M. p.	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl
Methyl *	128°/5	53°	56·5	4·1	20·8	$C_8H_7O_2Cl$	56·3	4·1	20·8
Ethyl	123°/5	64·5	58·6	4·9	19·1	$C_9H_9O_2Cl$	58·5	4·9	19·2
Propyl	118°/4	42	60·4	5·5	17·8	$C_{10}H_{11}O_2Cl$	60·5	5·6	17·8
Butyl	140°/3	27	62·2	6·2	16·6	$C_{11}H_{13}O_2Cl$	62·1	6·2	16·7
Pentyl	177°/9	32	63·5	6·7	15·7	$C_{12}H_{15}O_2Cl$	63·6	6·7	15·6
Hexyl	152°/4	30	64·9	7·0	14·7	$C_{13}H_{17}O_2Cl$	64·9	7·1	14·7
Heptyl	160°/4	34	66·1	7·4	14·1	$C_{14}H_{19}O_2Cl$	66·0	7·5	13·9
Octyl	151°/2	40	67·0	7·8	13·2	$C_{15}H_{21}O_2Cl$	67·0	7·9	13·2
Nonyl	189°/6	55	67·8	8·3	12·4	$C_{16}H_{23}O_2Cl$	67·9	8·2	12·5
Decyl	180°/2	54	68·8	8·5	11·9	$C_{17}H_{25}O_2Cl$	68·8	8·5	11·9
Dodecyl	189°/4	58·5	70·3	9·1	11·2	$C_{19}H_{29}O_2Cl$	70·2	9·0	10·9
Hexadecyl	216°/1	67·5	72·2	9·5	9·1	$C_{23}H_{37}O_2Cl$	72·5	9·8	9·3
Octadecyl	278°/2	71·5	73·1	9·8	8·9	$C_{25}H_{41}O_2Cl$	73·4	10·1	8·7

* Not new.

crude acids were crystallised from glacial acetic acid until the m. p.s were constant. After the first crystallisation the yields were about 70—90%, but about seven crystallisations were necessary to obtain samples satisfactory for transition-point determinations. The analyses are tabulated.

trans-*4-Alkoxy-3-chlorocinnamic acids.*

Alkyl	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl
Methyl	56·4	4·3	16·7	$C_{10}H_9O_3Cl$	56·4	4·3	16·7
Ethyl	58·3	4·9	15·7	$C_{11}H_{11}O_3Cl$	58·3	4·9	15·7
Propyl	60·3	5·4	14·7	$C_{12}H_{13}O_3Cl$	59·9	5·4	14·8
Butyl	61·6	6·0	13·6	$C_{13}H_{15}O_3Cl$	61·3	6·0	13·9
Pentyl	62·7	6·6	13·0	$C_{14}H_{17}O_3Cl$	62·4	6·4	13·2
Hexyl	64·1	6·9	12·6	$C_{15}H_{19}O_3Cl$	63·7	6·8	12·6
Heptyl	64·8	7·3	11·7	$C_{16}H_{21}O_3Cl$	64·7	7·1	12·0
Octyl	65·9	7·4	11·4	$C_{17}H_{23}O_3Cl$	65·7	7·4	11·4
Nonyl	66·8	7·7	10·9	$C_{18}H_{25}O_3Cl$	66·7	7·8	10·9
Decyl	67·6	8·1	10·4	$C_{19}H_{27}O_3Cl$	67·6	8·1	10·5
Dodecyl	69·4	8·6	9·7	$C_{21}H_{31}C_3Cl$	69·1	8·6	9·7
Hexadecyl	71·4	9·3	8·3	$C_{25}H_{39}O_3Cl$	71·3	9·3	8·4
Octadecyl	72·1	9·7	7·9	$C_{27}H_{43}O_3Cl$	72·2	9·7	7·9

4-n-*Alkoxy-3-bromobenzaldehydes.* The *p*-alkoxybenzaldehyde (0·1 mole), in carbon tetrachloride (15 ml.) containing a trace of iodine, was refluxed with bromine (16 g., 0·1 mole), with constant stirring, until no more hydrogen bromide was evolved, and the solution was pale straw-coloured. The cooled solution was washed successively with aqueous sodium hypobromite, water, saturated aqueous sodium carbonate, and water. The solvent was then removed from the dried extract under reduced pressure, and the residual crude solids were crystallised from ethanol and light petroleum. The lower ethers were rather difficult to crystallise, and the yields after one crystallisation varied between 50 and 70%. The m. p.s and analyses are tabulated.

4-Alkoxy-3-bromobenzaldehydes.

Alkyl	M. p.	Found (%) C	H	Br	Formula	Required (%) C	H	Br
Methyl *	53°	44·5	3·6	37·4	$C_8H_7O_2Br$	44·7	3·3	37·2
Ethyl	60·5	47·2	4·1	34·8	$C_9H_9O_2Br$	47·2	4·0	34·9
Hexyl	47	54·6	6·0	28·0	$C_{12}H_{17}O_2Br$	54·7	6·0	28·0
Heptyl	51	56·2	6·4	26·7	$C_{14}H_{19}O_2Br$	56·2	6·4	26·7
Octyl	55	57·7	6·9	25·4	$C_{15}H_{21}O_2Br$	57·5	6·8	25·5
Nonyl	59·5	58·9	7·3	24·2	$C_{16}H_{23}O_2Br$	58·7	7·1	24·4
Decyl	59·5	59·9	7·7	23·7	$C_{17}H_{25}O_2Br$	59·8	7·4	23·4
Dodecyl	66·5	61·7	8·2	21·7	$C_{19}H_{29}O_2Br$	61·8	7·9	21·6
Hexadecyl	72	64·5	8·7	19·1	$C_{23}H_{37}O_2Br$	64·9	8·8	18·8
Octadecyl	82·5	66·2	9·3	17·7	$C_{25}H_{41}O_2Br$	66·2	9·1	17·6

* Not new.

trans-4-n-*Alkoxy-3-bromocinnamic acids.* These *acids* were prepared in the same way as the analogous chloro-derivatives. After one crystallisation from glacial acetic acid the yields

were 75—85%. The acids were then crystallised from acetic acid, benzene, and toluene until their m. p.s and transition temperatures were constant. The analyses are annexed.

4-Alkoxy-3-bromocinnamic acids.

	Found (%)				Required (%)		
Alkyl	C	H	Br	Formula	C	H	Br
Methyl	46·7	3·7	31·1	$C_{10}H_9O_3Br$	46·7	3·5	31·1
Ethyl	48·9	4·4	29·6	$C_{11}H_{11}O_3Br$	48·7	4·1	29·5
Hexyl	55·4	6·2	24·3	$C_{15}H_{19}O_3Br$	55·1	5·8	24·5
Heptyl	56·4	6·4	23·2	$C_{16}H_{21}O_3Br$	56·3	6·2	23·5
Octyl	57·7	6·6	22·4	$C_{17}H_{23}O_3Br$	57·5	6·5	22·5
Nonyl	58·7	6·8	21·5	$C_{18}H_{25}O_3Br$	58·5	6·8	21·7
Decyl	59·7	7·0	20·8	$C_{19}H_{27}O_3Br$	59·5	7·0	20·9
Dodecyl	61·5	7·8	19·4	$C_{21}H_{31}O_3Br$	61·3	7·5	19·5
Hexadecyl	64·3	8·5	16·9	$C_{25}H_{39}O_3Br$	64·2	8·4	17·1
Octadecyl	65·4	8·7	16·2	$C_{27}H_{43}O_3Br$	65·5	8·7	16·2

4-Alkoxy-3-iodobenzaldehydes. The *p*-alkoxybenzaldehyde (0·05 mole) and iodine (16 g., 0·063 mole) were dissolved in ethanol (200 ml.). In the case of the hexadecyloxy- and octadecyloxy-aldehyde the volume of solvent was increased to 225 ml. Finely powdered mercuric oxide (16 g., 0·07 mole) was added, and the mixture vigorously stirred while concentrated sulphuric acid (5 ml., 94% w/w) was added dropwise during 15 min. Stirring was continued for 12 hr. at room temperature, whereupon the mixture was filtered. The filtrate was diluted with water (500 ml.) to precipitate the crude *4-alkoxy-3-iodobenzaldehydes*, saturated aqueous sodium thiosulphate (250 ml.) was added, and the suspension thoroughly stirred. The iodo-compound was separated in nearly quantitative yield by filtration, except for the oily butyl ether which was extracted with chloroform and recovered after drying (Na_2SO_4). The impure products were then crystallised from light petroleum (b. p. 40—60°) until their m. p.s were constant.

4-Alkoxy-3-iodobenzaldehydes.

		Found (%)				Required (%)		
Alkyl	M. p.	C	H	I	Formula	C	H	I
Methyl	110·5°	36·6	2·4	48·7	$C_8H_7O_2I$	36·7	2·7	48·4
Butyl	22	43·5	4·4	41·7	$C_{11}H_{13}O_2I$	43·4	4·3	41·7
Hexyl	34·5	47·2	5·1	37·9	$C_{13}H_{17}O_2I$	47·0	5·2	37·9
Heptyl	37	48·7	5·6	36·5	$C_{14}H_{19}O_2I$	48·6	5·5	36·7
Octyl	44	50·0	5·9	35·0	$C_{15}H_{21}O_2I$	50·0	5·9	35·2
Nonyl	47·5	51·1	6·4	33·7	$C_{16}H_{23}O_2I$	51·3	6·2	33·9
Decyl	52	52·8	6·6	32·7	$C_{17}H_{25}O_2I$	52·6	6·5	32·7
Dodecyl	59·5	54·9	7·2	30·5	$C_{19}H_{29}O_2I$	54·8	7·0	30·5
Hexadecyl	75	58·6	7·9	26·7	$C_{23}H_{37}O_2I$	58·5	7·9	26·9
Octadecyl	76·5	59·8	8·4	25·3	$C_{25}H_{41}O_2I$	60·0	8·3	25·4

trans-4-n-*Alkoxy-3-iodocinnamic acids.* The *acids* were prepared in the manner described for the analogous chloro-derivatives The amount of pyridine was increased to 14 ml. for the dodecyl, hexadecyl, and octadecyl ethers. The crude products were crystallised from glacial acetic acid (yield 90—95%), and then from benzene until constant m. p.s were obtained.

4-Alkoxy-3-iodocinnamic acids.

	Found (%)				Required (%)		
	C	H	I	Formula	C	H	I
Methyl	39·7	3·0	41·7	$C_{10}H_9O_2I$	39·5	3·0	41·7
Butyl	45·2	4·3	36·5	$C_{13}H_{15}O_2I$	45·1	4·4	36·7
Hexyl	48·2	5·3	33·7	$C_{15}H_{19}O_2I$	48·1	5·1	33·9
Heptyl	49·5	5·4	32·4	$C_{16}H_{21}O_2I$	49·5	5·5	32·7
Octyl	50·8	5·7	31·4	$C_{17}H_{23}O_2I$	50·8	5·8	31·6
Nonyl	51·9	6·0	30·4	$C_{18}H_{25}O_2I$	51·9	6·1	30·5
Decyl	52·9	6·2	29·4	$C_{19}H_{27}O_2I$	53·0	6·3	29·5
Dodecyl	55·3	6·8	27·5	$C_{21}H_{31}O_2I$	55·0	6·8	27·7
Hexadecyl	58·7	7·6	24·5	$C_{25}H_{39}O_2I$	58·4	7·6	24·7
Octadecyl	60·1	7·9	23·3	$C_{27}H_{43}O_2I$	59·8	8·0	23·4

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289. *The Conductivity of Solutions in which the Solvent Molecule is "Large." Part I. Solutions of Tetraethylammonium Picrate in Some Phthalate Esters.*

By C. M. French and N. Singer.

The conductances of tetraethylammonium picrate in six dialkyl phthalates at 25°, 35°, and 45° have been measured over concentration ranges from $1{\cdot}03 \times 10^{-5}$ to $2{\cdot}516 \times 10^{-3}$ mole/l. The shapes of the resulting conductance curves agree with the theories of conductance in solvents of fairly low dielectric constant. Variations in the value of the Walden product $\lambda_0\eta$ from solvent to solvent, and with temperature are reported. These are accounted for by a theory of solvent–solvent and solvent–ion interaction.

Walden has shown that in a large number of solvents the product $\lambda_0\eta$ for tetraethylammonium picrate is a constant, independent of temperature, and with a value 0·563. This led to the suggestion that the solute ions are unsolvated in such solvents, solvation occurring only in those solutions where the product is less than 0·563. Thus for example the values in pyridine 0·635 (ref. 1) or 0·648 (ref. 2) and in aniline 0·635 (ref. 3) require explanation. In their work on tetrabutylammonium picrate in tritolyl phosphate, Fuoss and Elliott [4] obtained a higher value than expected; this, they attempted to explain on the assumption that, since the solvent molecules here are larger than in the usual solvents, certain configurations of them should exist that would allow the solute ions to slip between the solvent molecules without having to overcome the full macroscopic viscosity. This would naturally result in a greater ionic mobility and hence in an abnormally large $\lambda_0\eta$ value. This explanation is clearly not valid for solutions in pyridine and aniline. The only other recorded measurements in solvents having large molecules (triethanolamine, and *N*-ethyl-*N*-phenylethanolamine) are those by Bhattacharyya and Nakhate.[5] It was therefore thought to be of interest to investigate the conductance, in a series of closely related solvents of gradually increasing molecular size, of tetraethylammonium picrate which obeys Walden's rule accurately in a number of solvents of normal size. The solvents chosen for this purpose were in the first instance the dialkyl phthalates, measurement being carried out at 25°, 35°, and 45°.

Experimental

The conductance of most of the solutions was measured by means of a Leeds and Northrup A.C. bridge of the Jones and Joseph type incorporating Wagner earthing. The source of alternating current was a tuned audiofrequency oscillator which was usually operated at 1000 cycles per sec. As detector a tuned audiofrequency amplifier was used in conjunction with a telephone of 30,000 ohms impedance at 1000 cycles. Leads were carefully screened.

The very high resistances obtained with the pure solvents and solutions of tetraethylammonium picrate in dioctyl and dinonyl phthalate were measured by means of a Schering bridge. The remainder of the ancillary apparatus was the same as before.

The cells used for the more highly conducting solutions were based on the design of Jones and Bollinger [6] and made of Pyrex. The electrodes were stout, circular, platinum discs, of about 3 cm. diameter and about 1·5 mm. apart. For the less conducting solutions the electrode system consisted of three concentric platinum cylinders, about 1 mm. apart, and was similar to that used by Fuoss and Kraus.[7] The cell itself consisted of an annular glass cylinder which contained the electrodes, and to the top of which were fused the tubes carrying the contact leads and the inlet tubes. This arrangement gave a cell with a small internal volume and,

[1] Walden, Audrieth, and Birr, *Z. phys. Chem.*, 1932, **160**, *A*, 337.
[2] Pickering and Kraus, *J. Amer. Chem. Soc.*, 1949, **71**, 3288.
[3] Walden and Audrieth, *Z. phys. Chem.*, 1933, **165**, *A*, 11.
[4] Elliott and Fuoss, *J. Amer. Chem. Soc.*, 1939, **61**, 294.
[5] Bhattacharyya and Nakhate, *J. Indian Chem. Soc.*, 1947, **24**, 90.
[6] Jones and Bollinger, *J. Amer. Chem. Soc.*, 1931, **53**, 411.
[7] Fuoss and Kraus, *ibid.*, 1933, **55**, 3614.

because of the large surface area presented to the thermostat oil, led to a rapid attainment of temperature equilibrium. The cells were immersed in liquid white paraffin in a thermostat at 25° ± 0·02°. Between measurements, cells were cleaned by allowing them to stand in hot concentrated nitric acid, then steaming them out, rinsing them with acetone, and drying them in an oven. Cell constants were determined by the Ives and Sames's method,[8] with a standard solution of benzoic acid, usually 10^{-4}N.

The solvents used were purified as follows: Dimethyl, diethyl, dibutyl, and dipentyl phthalate were washed first with sodium carbonate solution, then with distilled water, dried ($CaCl_2$), and distilled 3 times under reduced pressure, only the middle fraction being collected

TABLE 1. *Physical properties of alkyl phthalates.* (The first row for each ester gives the values found; other rows give the values from the literature.)

Phthalate	Sp. cond., κ, (mho)	n_D^{20}	Viscosity, η (centipoises), at 25°	35°	45°	d_4^{25}	d_4^{35}	d_4^{45}	Dielectric const. at 25°	35°	45°
Me_2	8·1 × 10^{-9}	1·5149	13·92	9·18	6·41	1·1865	1·1775	1·1674	8·37	8·25	8·11
		1·5138[a]	13·8[c]	8·9[d]	6·3[c]	1·190[a]	1·1789[d]				
		1·5160[b]		9·2[e]							
Et_2	1·1 × 10^{-9}	1·5022	10·82	7·63	5·57	1·1160	1·1079	1·0991	7·53	7·34	7·13
			10·6[c]	7·6[c]	5·5[c]	1·1172[f]	1·1083[f]	1·0995			
			10·06[e]			1·1142[e]					
			10·0[a]			1·118[a]					
Bu_2	9 × 10^{-11}	1·4929	16·55	11·17	7·95	1·0426	1·0345	1·0264	6·36	6·17	5·99
		1·49292[b]	16·7[c]	11·4[c]	8·1[c]	1·0416[b]	1·0331[b]	1·0256[b]			
$(C_5H_{11})_2$	6·2 × 10^{-12}	1·4885	27·58	17·03	11·51	1·0230	1·0132	1·0025	5·96	5·79	5·62
		1·488[e]				1·022—1·025[e]					
$(CH_2{\cdot}CHEtBu)_2$	7·4 × 10^{-13}	1·4863	58·22	33·67	21·40	0·9803	0·9731	0·9656	5·06	4·91	4·77
		1·484—1·485†[e]	81·4‡			0·986[d]					
$(C_9H_{19})_2$ *	9·6 × 10^{-14}	1·4825	77·90	43·14	27·12	0·9640	0·9570	0·9501	4·89	4·65	4·52

* Mixture of isomers, mostly 3 : 5 : 5-trimethylhexyl. † At 25°. ‡ At 20°.

[a] Gardner and Brewer, *Ind. Eng. Chem.*, 1937, **29**, 179. [b] Von Auwers and Heinze, *Ber.*, 1919, **52**, 600. [c] Jones, "Plasticizers, Fillers, Catalysts and Accelerators," Inst. Plastics Ind., 1947, No. 11, p. 24. [d] Swirbely, Eareckson, Matsuda, Pickard, Solet, and Tuemmler, *J. Amer. Chem. Soc.*, 1949, **71**, 507. [e] Buttrey, "Plasticizers," Cleaver-Hulme Press Ltd., London, 1950, pp. 5, 6, 11, 13. [f] Perkin, *J.*, 1896, **69**, 477. [g] Baker, *J.*, 1913, **103**, 166. [h] Berko and Bradley, *Proc. Roy. Soc.*, 1949, *A*, **198**, 226.

each time. The pure liquids were stored in a vacuum-desiccator (P_2O_5). Di-(2-ethylhexyl) and dinonyl phthalate were washed with sodium carbonate solution and then shaken with water; the resulting emulsion was broken by addition of ether. The ethereal solution was twice washed with water, dried ($CaCl_2$), and evaporated, and the residual liquid distilled 3 times under reduced pressure. The pure liquids were stored in a vacuum-desiccator (P_2O_5). The physical constants of these liquids are given in Table 1.

Conductivity water was prepared by running distilled water through a Biodeminrolit ion-exchange resin column. The resulting water had a specific conductance of 0·8—1·0 × 10^{-6} mho.

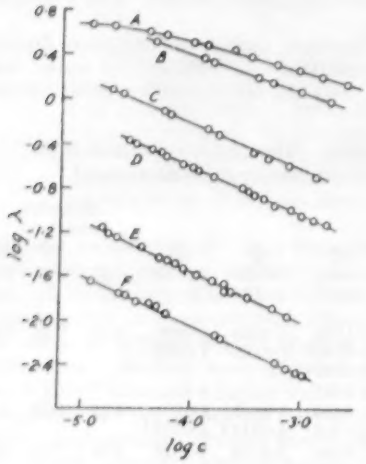
"AnalaR" benzoic acid was further purified by recrystallisation and sublimation at about 110°; it had m. p. 122° (lit., 122·38° [9]).

Tetraethylammonium picrate was prepared by interaction between hot aqueous solutions of the recrystallised tetraethylammonium bromide and silver picrate (prepared by the addition of picric acid to a suspension of silver oxide). The resulting salt was recrystallised 4 times from alcohol–ether, dried at 80°, and stored in a vacuum-desiccator (P_2O_5). It had m. p. 256·5—257° (lit., 255·8° [10]).

Results.—Table 1 records physical properties for the solvents, and recorded values where available.

[8] Ives and Sames, *J.*, **1943**, 511.
[9] Swab and Vickers, *J. Res. Nat. Bur. Stand.*, 1941, **34**, 333.
[10] Walden, Ulich, and Laun, *Z. phys. Chem.*, 1925, **114**, *A*, 286.

The Figure illustrates the variation in equivalent conductance, with concentration, of tetraethylammonium picrate in the six solvents at 25°. The curves at the other temperatures are similar. The exact experimental data for all systems are given in Table 2.



Phthalates: A, dimethyl; B, diethyl; C, dibutyl; D, dipentyl; E, di-(2-ethylhexyl); F, di "nonyl."

Discussion

In all cases the shapes of the λ–$\sqrt{c}$ curves (where λ is the equivalent conductance, and c is the concentration in moles/l.) can be completely explained on the basis of the formation of ion pairs in the dilute regions, and of triple ions in the more concentrated solutions. The progressive decrease in slope of the linear (log λ–log c) plots to a limiting value of $-\frac{1}{2}$ with decrease in dielectric constant expected on this basis was obtained in all the systems studied. Thus the slopes decrease from about −0·28 for solutions in dimethyl phthalate of dielectric constant 8·6, to −0·46 for solutions in dinonyl phthalate of dielectric constant 4·9, both at 25°. Similar results are obtained at the other temperatures.

A value for the limiting equivalent conductance and for the dissociation constant for ion-pair formation in each system, was obtained by Shedlovsky's graphical extrapolation method,[11] and the results are shown in Table 3 together with the corresponding values of the Walden product.

Points requiring explanation are: (1) $\lambda_0\eta$ decreases with increasing size of the solvent molecule, being greater than the "normal" value in dimethyl—dipentyl phthalate, and less in the other two solvents. The direction of this change is the reverse of that expected on the basis of Fuoss and Elliott's [4] explanation. (2) $\lambda_0\eta$ increases with increase in temperature when the solvent molecule is large. The critical size of the solvent molecule at which this effect occurs may depend also on the size of the solute ions and, for the system reported here, it is only present in the three largest solvents, as seen from Table 3. (3) The equilibrium constant for ion-pair formation decreases less rapidly from dimethyl to dinonyl phthalate than expected from the dielectric constants of these solvents. These variations can be accounted for in a general way by ion-solvent interaction. In a dipolar solvent, a solute ion will be surrounded by, and associated with, a number of solvent molecules. All types of solvation from chemical binding to the formation of a labile complex due to Coulomb forces between the charge on the ion and the dipoles of the solvent are generally possible. In the present systems solvation would be restricted to the loose association of a number of solvent molecules with each ion, with the consequent hindering of its passage through solution. The extent of such solvation would depend on the dipole

[11] Shedlovsky, *J. Franklin Inst.*, 1938, **225**, 739.

TABLE 2. *Equivalent conductance (λ) of tetraethylammonium picrate in alkyl phthalates.*

Me_2 phthalate		Et_2 phthalate		Bu_2 phthalate		$(C_5H_{11})_2$ phthalate		$(C_8H_{17})_2$ phthalate		$(C_9H_{19})_2$ phthalate	
10^4c	λ	10^4c	λ	10^4c	λ	10^4c	10λ	10^4c	10λ	10^4c	$10^2\lambda$
Temperature: 25°.											
25·16	1·294	18·03	0·8735	13·72	0·1950	16·81	0·6943	7·618	0·1080	10·09	0·3086
14·58	1·497	9·456	1·105	7·651	0·2436	13·17	0·7505	5·446	0·1246	9·354	0·3184
8·730	1·728	5·206	1·330	4·976	0·2856	9·996	0·8669	3·183	0·1561	7·305	0·3663
5·725	1·956	3·880	1·516	3·812	0·3254	8·117	0·9318	2·203	0·1823	5·928	0·3940
3·211	2·297	1·470	2·064	1·699	0·4506	5·604	1·065	2·048	0·1909	1·905	0·6548
2·235	2·545	1·227	2·275	1·368	0·5060	3·689	1·297	1·977	0·1953	1·873	0·6597
1·270	2·922	0·4339	3·183	0·5916	0·7103	3·250	1·404	1·551	0·2188	1·763	0·6845
0·9253	3·175			0·5465	0·7315	3·061	1·439	1·116	0·2539	0·5861	1·120
0·5274	3·550			0·2207	1·066	1·526	1·934	0·7936	0·2961	0·4622	1·269
0·3818	3·773			0·1806	1·142	1·067	2·280	0·6840	0·3183	0·3975	1·328
0·1732	4·277					1·018	2·305	0·5783	0·3400	0·3091	1·480
0·1169	4·435					0·8239	2·450	0·5074	0·3621	0·2398	1·655
						0·5481	2·984	0·3489	0·4390	0·2248	1·697
						0·4993	3·107	0·2353	0·5054	0·1187	2·241
						0·4409	3·327	0·1676	0·5593		
						0·3011	3·863	0·1484	0·6310		
						0·2724	4·002	0·1030	0·7439		
Temperature: 35°.											
24·96	1·943	17·90	1·247	13·61	0·2921	16·65	1·108	7·561	0·1919	10·02	0·5863
14·46	2·255	9·386	1·578	7·591	0·3658	13·04	1·228	5·405	0·2217	9·286	0·6029
8·658	2·595	5·168	1·898	4·938	0·4439	9·901	1·396	3·160	0·3204	7·252	0·6793
5·679	2·952	3·85	2·171	3·783	0·4875	8·040	1·507	2·187	0·3210	5·885	0·7423
3·185	3·464	1·459	2·949	1·686	0·6727	5·550	1·763	2·033	0·3393	1·891	1·196
2·217	3·847	1·218	3·251	1·358	0·7541	3·653	2·082	1·962	0·3452	1·859	1·199
1·259	4·408	0·4308	4·535	0·5870	1·067	3·218	2·220	1·540	0·3764	1·750	1·257
0·9177	4·799			0·5423	1·068	3·032	2·277	1·108	0·4367	0·5818	2·106
0·5231	5·359			0·2190	1·594	1·512	3·056	0·7877	0·5096	0·4589	2·313
0·3787	5·730			0·1792	1·742	1·057	3·556	0·6789	0·5625	0·3946	2·499
0·1717	6·489					1·009	3·626	0·5740	0·6084	0·3069	2·786
0·1160	6·746					0·8160	3·930	0·5036	0·6451	0·2381	3·106
						0·5429	4·712	0·3463	0·7389	0·2231	3·204
						0·4945	4·902	0·2335	0·9174	0·1179	4·264
						0·4366	5·167	0·1663	0·9590		
						0·2983	6·070	0·1472	1·088		
						0·2698	6·393	0·1022	1·283		
Temperature: 45°.											
24·76	2·725	17·76	1·694	13·50	0·4157	16·47	1·661	7·503	0·3165	9·942	1·011
14·34	3·174	9·312	2·148	7·532	0·5224	12·90	1·842	5·364	0·3657	9·219	1·043
8·589	3·645	5·128	2·583	4·899	0·6058	9·795	2·088	3·135	0·4561	7·200	1·176
5·634	4·161	3·821	2·951	3·753	0·6990	7·954	2·260	2·170	0·5296	5·842	1·279
3·159	4·877	1·448	4·009	1·673	0·9528	5·491	2·644	2·017	0·5570	1·877	2·136
2·199	5·434	1·209	4·415	1·347	1·074	3·614	3·119	1·947	0·5701	1·738	2·223
1·249	6·233	0·4274	6·147	0·5824	1·516	3·184	3·329	1·528	0·6377	0·5776	3·672
0·9104	6·788			0·5381	1·519	3·000	3·415	1·099	0·7402	0·4552	4·000
0·5189	7·569			0·2173	2·265	1·496	4·573	0·7817	0·8639	0·3918	4·333
0·3756	7·990			0·1778	2·425	1·045	5·333	0·6737	0·9251	0·3047	4·930
0·1704	9·136					0·9978	5·439	0·5696	0·9995	0·2363	5·537
0·1150	9·502					0·8073	5·944	0·4997	1·056	0·2215	5·724
						0·5371	7·069	0·3436	1·254	0·1169	7·459
						0·4893	7·354	0·2317	1·510		
						0·4320	7·751	0·1651	1·757		
						0·2951	9·108	0·1461	1·847		
						0·2669	9·539	0·1014	2·179		

TABLE 3.

Phthalate	10^2K at			λ_o (ohm^{-1} cm.^{2}) at			$\lambda_o\eta$ at		
	25°	35°	45°	25°	35°	45°	25°	35°	45°
Me_2	467·7	497·7	494·3	5·05	7·73	10·96	0·703	0·710	0·703
Et_2	158·1	168·3	159·2	6·52	9·30	12·63	0·705	0·710	0·704
Bu_2	18·32	21·14	18·58	5·92	5·81	8·15	0·649	0·648	0·655
$(C_5H_{11})_2$	10·64	8·53	7·91	2·08	3·57	5·54	0·574	0·608	0·639
$(C_8H_{17})_2$	8·87	5·78	4·41	0·276	0·588	1·12	0·162	0·198	0·239
$(C_9H_{19})_2$	7·31	5·58	3·13	0·117	0·263	0·465	0·092	0·114	0·126

moment of the solvent, the size of the ion, the distance of closest approach of the ion to the solvent dipole, and the dielectric constant of the solvent.

Although Walden ascribed the observed constancy of $\lambda_0\eta$ in solvents of dielectric constant 10—35 to non-solvation, uniform solvation would lead to the same result. Considerations just noted suggest that large ions such as Et_4N^+ are solvated, so that a

TABLE 4.

	Ion-pair size (10^{-8} cm.) at				Ion-pair size (10^{-8} cm.) at		
Phthalate	25°	35°	45°	Phthalate	25°	35°	45°
Me_2	5·86	5·70	5·65	$(C_5H_{11})_2$	6·03	5·85	5·85
Et_2	5·80	5·85	5·83	$(C_8H_{17})_2$	7·33	7·00	6·81
Bu_2	5·84	5·82	5·85	$(C_9H_{19})_2$	7·62	7·49	7·21

" normal " value of $\lambda_0\eta$ here may be due to a mutual compensation of changes in the above factors within certain limits. It might then be expected that the Walden product would be subject to specific solvent effects.

Dimethyl phthalate has a large dipole moment[12] (2·3; 2·8 D), and its dielectric constant is low. It may therefore be assumed that the pure ester is associated in such a way that the dipoles are as close together as possible and will be shielded from close approach by, or interaction with, the solute ions. The solute ions may accordingly be regarded as practically unsolvated in this solvent [and also in diethyl phthalate (dipole moment 2·4; 2·7; 2·8)]. As the bulk of the alcohol residue in the ester increases, it will become increasingly difficult for two solvent molecules to approach each other closely, and their interaction energy will therefore decrease. This type of solvent association will decrease progressively from dibutyl to dinonyl phthalate. Ion solvation will then increase and $\lambda_0\eta$ decrease in the same direction. Further, $\lambda_0\eta$ will be smaller in these large molecule solvents than in normal systems.

The large size of the ions and of the solvating molecules in these systems will result in a small interaction energy between the two. A slight increase in temperature will therefore be sufficient to decrease the amount of solvation significantly. The $\lambda_0\eta$ product should thus increase with increase in temperature, as is found with the three largest solvents (Table 3). The absence of this temperature effect in the two smallest solvents would be consistent with the suggestion above, that the solute ions are practically unsolvated in these solvents. Dibutyl phthalate thus appears to be the solvent molecule of critical size for these phenomena in the present systems.

Comparison of the present $\lambda_0\eta$ values with those of similar systems further supports the explanation offered here. Thus $\lambda_0\eta$ for tetraethylammonium picrate in both pyridine [1] (ε_{25} 12·01) and aniline [2] (ε_{25} 7·2) is of the order of 0·650. Although both these solvents and the phthalates have strong localised dipoles, yet if solvent association occurs shielding of the dipoles in the latter systems will be more complete, and $\lambda_0\eta$ might therefore be expected to be correspondingly greater. This is verified experimentally with dimethyl and diethyl phthalate as solvent. Conversely, a normal result would be expected, and is found, in ethylene dichloride [13] (ε_{25} 10·1; $\lambda_0\eta$ 0·545) and ethylidene chloride [14] (ε_{25} 10·00; $\lambda_0\eta$ 0·542), where, even if solvent association occurs, the geometry of the molecule precludes shielding of the dipole from an approaching ion. Fuoss and Elliott's results [4] are explicable on the same basis, tritolyl phosphate having a strong localised dipole which is shielded if solvent association occurs.

This kind of solvent association will only occur if the solvent is of fairly low dielectric constant, when the forces between the dipoles will be large. Thus a normal $\lambda_0\eta$ value would be expected, and is found, in such solvents as nitrobenzene [15] (0·586) and in acetophenone [16] (0·591).

[12] Wesson, " Tables of Electric Dipole Moments," Technology Printers, Cambridge, Mass., 1949.
[13] Walden and Busch, *Z. phys. Chem.*, 1929, **140**, *A*, 89.
[14] Healey and Martell, *J. Amer. Chem. Soc.*, 1951, **73**, 3296.
[15] Taylor and Kraus, *ibid.*, 1947, **69**, 1731.
[16] Walden and Birr, *Z. phys. Chem.*, 1933, **165**, *A*, 32.

Finally the theory of ion-pair formation leads to the familiar equation for the equilibrium constant :

$$\frac{1}{K} = \frac{4\pi N}{1000}\left[\frac{\epsilon^2|Z_1Z_2|}{DkT}\right]^3 . Q(b)$$

where $b = \frac{|Z_1Z_2|\epsilon^2}{aDkT}$ and a is the radius of the ion pair and the other symbols have their usual significance. By using these two equations, a graph of log b against log $Q(b)$, and the values of K given in Table 3, the a values in the various solvents may be computed. The results are shown in Table 4, and demonstrate the gradual increase in size of the ion pair in the series of solvents from dimethyl to dinonyl phthalate.

The suggestions offered here are clearly an over-simplification, but nevertheless they afford a qualitative explanation for differences in behaviour of a number of systems, including those in which the solvent molecule is large. It is hoped that further work on large solvent molecule systems now in progress will clarify other points.

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Mile End Road, London, E.1. [*Received, November 11th*, 1955.]

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290. *New Intermediates and Dyes. Part IV.* Condensation of Thionaphthen-2 : 3-dicarboxylic Anhydride with Hydrocarbons and Phenols.*

By Arnold T. Peters and Derek Walker.

Thionaphthen-2 : 3-dicarboxylic acid anhydride (I) and its 6-chloro-4-methyl derivative were condensed with acenaphthene to give 3-(3-acenaphthenylcarbonyl)thionaphthen-2-carboxylic acids, which could not be cyclised. The anhydride (I) reacted with phenol to yield a phenolphthalein analogue, or with quinol to give 6 : 11-dihydro-7 : 10-dihydroxy-6 : 11-dioxo benzo[*b*]thiophanthrene (III). Resorcinol and the anhydride (I) afforded a fluorescein analogue and also 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid; the chemistry of this acid was examined and several lactones were derived from it.

Dyes for cellulose acetate and Nylon were prepared from the dione (III), and their properties compared with those of their anthraquinone analogues; loss of tinctorial power occurs on introduction of the thionaphthen ring.

The object of the present work was to investigate the nature of intermediates and dyes derived from the anhydride (I).

Mayer [1] showed that the anhydride reacted in a similar manner to phthalic anhydride, condensation with simple aromatic hydrocarbons in the Friedel-Crafts reaction giving solely 3-aroylthionaphthen-2-carboxylic acids, cyclisation yielding the corresponding 6 : 11-dihydro-6 : 11-dioxobenzo[*b*]thiophanthrenes.

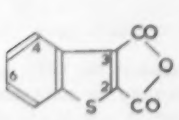
Both thionaphthen-2 : 3-dicarboxylic acid anhydride and its 6-chloro-4-methyl derivative were condensed with acenaphthene to give 3-(3-acenaphthenylcarbonyl)thionaphthen-2-carboxylic acid (II) and its 6-chloro-4-methyl derivative, respectively. Neither carboxylic acid could be cyclised, although a variety of methods was used.

We prepared 6 : 11-dihydro-7 : 10-dihydroxy-6 : 11-dioxobenzo[*b*]thiophanthrene † (III) by the method of Mayer and Zahn,[2] *i.e.*, by heating the anhydride (I) with quinol in an

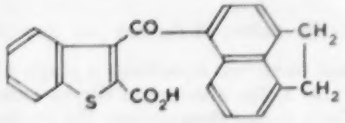
* Part III, *J.*, 1952, 1368.
† Cf. Ring Index No. 2502.

[1] Mayer (with Mombour, Lassmann, Werner, Landmann, and Schneider), *Annalen*, 1931, **488**, 259.
[2] Mayer and Zahn, G.P. 512,237/1927; B.P. 296,761/1927; U.S.P. 1,765,687/1930.

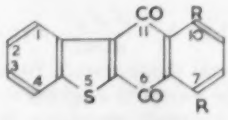
aluminium chloride–sodium chloride melt, and found it to be purified best through the crystalline diacetate. By condensing the anhydride (I) with *p*-chlorophenol, we obtained a 31% yield of 7(or 10)-chloro-10(or 7)-hydroxy-6 : 11-dioxobenzo[*b*]thiophanthrene, also purified through the acetoxy-compound.



(I)



(II)

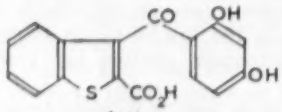


(III): R = OH
(IV): R = NHMe or NHBu^n

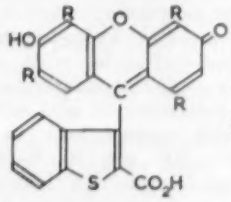
6 : 11-Dihydro-7 : 10-dihydroxy-6 : 11-dioxobenzo[*b*]thiophanthrene was only sparingly soluble in aqueous alkalis (contrast Mayer and Zahn [2]); its solution in pyridine assumed an intense royal blue colour when treated with a variety of aliphatic amines. The dione was readily converted into the 7 : 10-bismethylamino- and 7 : 10-bis-*n*-butylamino-compounds (IV) by heating it with sodium dithionite [hydrosulphite] and an alcoholic solution of the appropriate amine in a sealed tube at 140—145° and 135—140°, respectively; the dithionite assists the conversion by reducing part of the anthraquinone derivative to the corresponding *leuco*-compound.

The hitherto unknown 1 : 4-di-*n*-butylaminoanthraquinone was also prepared by a similar method from quinizarin, for comparison. The new dyes (IV) were best purified by chromatography. Both dye cellulose acetate and Nylon a pale greenish-blue, weaker than the royal blues produced by 1 : 4-bismethylamino- and 1 : 4-bis-*n*-butylamino-anthraquinone. Thus the introduction of the thiophen ring in the above manner caused loss in tinctorial power.

By condensing the anhydride (I) with resorcinol, Mayer [1] obtained a fluorescein derivative, which was not purified. We have studied the interaction of the anhydride (I) and resorcinol in the presence of zinc chloride at 150—210°, and two pure compounds, one red and one yellow, were isolated from the resinous reaction mass; a summary of the results is given in the Table on p. 1434. At the lower temperatures, the products were contaminated with much starting material, and the best separation of the products was obtained after reaction at 165—175°; at 210°, relatively high yields of the red fluorescein analogue were formed. Chemical evidence and analysis of the yellow compound, and also of its dibromo-derivative, suggested that it was a benzoyldihydroxythionaphthencarboxylic acid. As Mayer [1] had shown that the anhydride (I) condensed with aromatic compounds to yield solely 3-aroylthionaphthen-2-carboxylic acids, and as the condensation of phthalic anhydride with resorcinol was proved by Heller [3] to give 2-(2 : 4-dihydroxybenzoyl)benzoic acid, the above yellow compound was probably 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid (V), convertible into its dibromo-derivative. In the view of Orndorff and



(V)



(VI): R = H
(VII): R = Br

Kline,[4] 2-(2 : 4-dihydroxybenzoyl)benzoic acid is an intermediate in the formation of fluorescein. If formula (V) is correct, then the derived fluorescein and eosin derivative can be designated as (VI) and (VII) respectively.

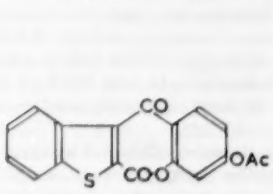
[3] Heller, *Ber.*, 1895, **28**, 312.
[4] Orndorff and Kline, *J. Amer. Chem. Soc.*, 1924, **46**, 2276.

The ultraviolet absorption spectra of the red fluorescein analogue and of fluorescein itself are very similar, and quite different from that of 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid.

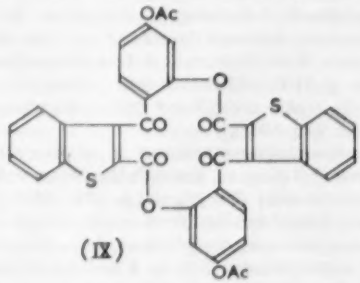
Further investigation of the last-named acid and of its dibromo-derivative led to interesting results. Neither acid could be cyclised by standard procedures; both formed insoluble lead, silver, and mercuric salts, and the copper and barium salts were soluble in hot but insoluble in cold water. 3-(2 : 4-Dihydroxybenzoyl)thionaphthen-2-carboxylic acid behaved as a monobasic acid towards methyl-red (titrated in aqueous alcohol with 0·1N-alkali) but as a dibasic acid towards phenolphthalein: we found 2 : 4-dihydroxybenzoyl-*o*-benzoic acid to behave similarly.

When 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid was refluxed with acetic anhydride alone, or with acetyl chloride in an inert solvent, a yellow compound, $C_{18}H_{10}O_5S$, insoluble in sodium hydrogen carbonate solution and in cold aqueous sodium hydroxide, was obtained. This acetylation product dissolved rapidly in warm aqueous sodium hydroxide, and acidification then gave the above carboxylic acid. The yellow compound crystallised unchanged from benzene: in addition to acetylation, anhydride formation had occurred, to yield probably one of the two compounds (VIII) and (IX). Both such types have been recorded: Orndorff and Kline [4] claimed that, when 2-(2 : 4-dihydroxybenzoyl)benzoic acid was refluxed in acetic anhydride alone, the lactone (X) was formed, whereas the lactide resulted when the pure acid was refluxed in acetyl chloride.

Baker and his co-workers [5] have shown that both 2-carboxy-2′-hydroxybenzophenone and its 5′-methyl derivative yielded simple lactones with acetic anhydride, but gave lactides with phosphoric oxide, phosphorus oxychloride, or trifluoroacetic anhydride; the lactones were much more readily hydrolysed than the lactides. The use of acetic anhydride in the present work probably gave the lactone (VIII), which shows properties similar to



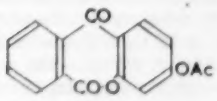
(VIII)



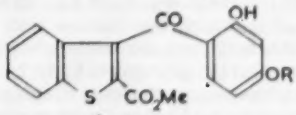
(IX)

those of other lactones.[4, 5] The lactone (VIII) is very readily hydrolysed, even by boiling water; when crystallised from methyl alcohol it afforded the methyl ester (XI), thus resembling the lactone (X).

When 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid was refluxed with acetyl chloride in an inert solvent, the lactone (VIII) and a product sparingly soluble in

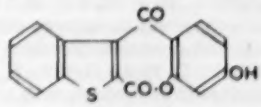


(X)



(XI): R = Ac

(XIII): R = H



(XII)

benzene resulted; the latter was not isolated when a large excess of acetyl chloride was used and is probably an intermediate in the formation of the lactone (VIII), into which it can be converted by acetyl chloride. The new product is insoluble in aqueous sodium hydrogen carbonate but soluble in aqueous sodium hydroxide, and is the lactone (XII) of

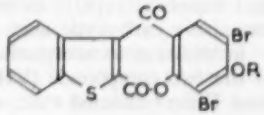
[5] Baker, Clark, Ollis, and Zealley, *J.*, 1952, 1452.

3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid; it was prepared in 93% yield by refluxing the acid with thionyl chloride in an inert solvent and is readily hydrolysed by aqueous alkalis.

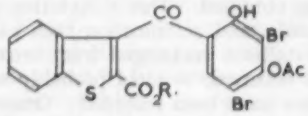
Crystallisation of the lactone (XII) from methyl alcohol gave the methyl ester (XIII), also prepared by the Fischer–Speier method from 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid.

Benzoyl chloride in an inert solvent converted 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid into the benzoylated lactone, analogous to the lactone (VIII).

3-(3 : 5-Dibromo-2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid behaved in identical manner to the unbrominated acid. Thus, acetyl chloride in an inert solvent converted it into the easily hydrolysable lactone (XIV), which on crystallisation from aqueous acetic acid gave the acetate (XV) or from methanol afforded the methyl ester (XVI).



(XIV): R = Ac
(XVII): R = H



(XV): R = H
(XVI): R = Me

When the dibromo-acid was refluxed with thionyl chloride in an inert solvent, the simple lactone (XVII) resulted.

Experimental

Thionaphthen-2 : 3-dicarboxylic Anhydride (I) (cf. Friedländer and his co-workers [6]).—Sodium 3-hydroxythionaphthen-2-carboxylate (80 g.) was converted through 3-hydroxythionaphthen into 2 : 3-dihydro-2 : 3-dioxothionaphthen (31·7 g.), golden-yellow prisms (from ethanol), m. p. 119°, and thence into thionaphthen-2 : 3-dicarboxylic acid (30·3 g.) and into its anhydride (I), which crystallised from acetic anhydride in stout, colourless needles, m. p. 171° (overall yield, 25 g., 33%).

6-Chloro-4-methylthionaphthen-2 : 3-dicarboxylic Anhydride.—6-Chloro-3-hydroxy-4-methylthionaphthen (7·9 g.) gave, through the dione, yellow needles (from methanol), m. p. 129—130°, the dicarboxylic acid (7·6 g.), m. p. 259—260° (from acetic acid), and thence the anhydride (6·8 g.), light brown needles (from acetic anhydride), m. p. 188—189°.

3-(3-Acenaphthenylcarbonyl)thionaphthen-2-carboxylic Acid (II).—Aluminium chloride (10 g., 2·2 mols.), acenaphthene (5·25 g., 1 mol.), and thionaphthen-2 : 3-dicarboxylic anhydride (7 g., 1 mol.) in dry nitrobenzene (50 ml.) were stirred at room temperature for 2 days. After decomposition of the mixture with ice and hydrochloric acid, the nitrobenzene was distilled with steam; the residue was extracted with boiling 7% aqueous sodium carbonate and then with boiling water (the sodium salt is only sparingly soluble). The extracts were treated with charcoal, filtered, and allowed to cool; the *sodium salt* of the acid (II) then crystallised in colourless leaflets, m. p. 320° (decomp.) (Found: C, 69·4; H, 3·4; Na, 6·1. $C_{23}H_{13}O_3SNa$ requires C, 69·5; H, 3·4; Na, 6·0%). The *acid* (II) (10·5 g., 82·3%) was obtained by refluxing the sodium salt in aqueous ethanol containing hydrochloric acid, or by refluxing it with acetic acid, and crystallisation from acetic acid gave colourless needles, m. p. 274—275° (decomp.) (Found: C, 73·2; H, 4·2; S, 8·9. $C_{23}H_{14}O_3S$ requires C, 73·7; H, 3·9; S, 8·9%). The acid dissolves in 20% oleum with a deep blue colour, changing to reddish-brown at room temperature in 30 min. The *methyl ester*, prepared by the Fischer–Speier method, crystallised from methanol in colourless needles, m. p. 157° (Found: S, 8·5. $C_{23}H_{16}O_3S$ requires S, 8·6%).

3-(3-Acenaphthenylcarbonyl)-6-chloro-4-methylthionaphthen-2-carboxylic Acid.—By the above procedure, acenaphthene (3·0 g., 1 mol.) and 6-chloro-4-methylthionaphthen-2 : 3-dicarboxylic anhydride (5·0 g., 1 mol.) gave the *sodium salt* (Found: Cl, 8·5; S, 7·7; Na, 5·4. $C_{25}H_{14}O_3ClSNa$ requires Cl, 8·3; S, 7·5; Na, 5·4%), converted into the *acid* (6·2 g., 77%), which crystallised from ethanol in colourless needles, m. p. 289—290° (Found: Cl, 8·3; S, 7·4. $C_{23}H_{15}O_3ClS$ requires Cl, 8·7; S, 7·9%).

[6] Friedländer, Bezdrick, and Koeniger, *Ber.*, 1908, **41**, 237.

Attempted Cyclisation of 3-(3-*Acenaphthenylcarbonyl*)*thionaphthen*-2-*carboxylic Acid and its* 6-*Chloro*-4-*methyl Derivative.*—The following reagents were tried on both carboxylic acids: sulphuric acid and 20% oleum at room temperature, phosphoric oxide at 120°, aluminium chloride on the acid chloride in carbon disulphide at room temperature or in nitrobenzene at 120—130°, and molten aluminium chloride–sodium chloride at 150—180°. Further methods tried with the acid (II) included benzoyl chloride in chloronaphthalene at 200° (Beyer and Richter [7]), boiling benzoyl chloride for 1 hr., and boiling acetic anhydride for 10—24 hr. In no case was a cyclised product isolated; water-soluble products resulted from the sulphuric acid experiments and the only other products isolated were unchanged material or intractable resins.

Condensation of the Anhydride (I) *with Phenol: Phenolphthalein Analogue.*—Thionaphthen-2 : 3-dicarboxylic anhydride (2 g., 1 mol.), phenol (3·7 g., 4 mols.), and anhydrous zinc chloride (5·4 g., 4 mols.) were heated together at 120° for 2 hr.; the temperature was raised to 160° during 1 hr. and kept thereat for a further 3 hr. The dark red product was extracted with ethanol, and the solution treated with cold water; a black tar was deposited; the liquor was decanted, water added to it, and phenol distilled off with steam. A yellow solid, m. p. 220—225°, was deposited from the residual solution during several days (the filtrate from it was shown to contain some thionaphthen-2 : 3-dicarboxylic acid). The solid was purified by boiling its ethanol solution with charcoal and adding it to water, collecting the solid, and then boiling this in 10% aqueous sodium hydroxide solution, filtering the mixture, and acidifying the alkaline filtrate with hydrochloric acid. Both processes were repeated; the final yellow amorphous solid had m. p. 228—231° (Found: S, 8·6. $C_{22}H_{14}O_5S$ requires S, 8·2%). The *phenolphthalein analogue* dissolves in aqueous sodium hydroxide to a deep and permanent bluish-red solution.

Reaction of Anhydride (I) *with Quinol:* 6 : 11-*Dihydro*-7 : 10-*dihydroxy*-6 : 11-*dioxobenzo*[b]-*thiophanthrene* (III).—To a stirred melt of aluminium chloride (50 g.) and sodium chloride (10 g.) at 160° was added a powdered mixture of thionaphthen-2 : 3-dicarboxylic anhydride (10 g.) and quinol (10 g.); the temperature was raised to 190° and kept there for 6 hr. After decomposition of the dark red mass with dilute hydrochloric acid and filtration, the solid was treated with boiling acetic anhydride (450 ml.) and a few drops of concentrated sulphuric acid, to give 7 : 10-*diacetoxy*-6 : 11-*dihydro*-6 : 11-*dioxobenzo*[b]*thiophanthrene*, which crystallised from acetic acid in bright yellow needles, m. p. 241—242° (Found: C, 63·4; H, 3·2; S, 8·4. $C_{20}H_{12}O_6S$ requires C, 63·2; H, 3·2; S, 8·4%). The dihydroxy-diketone was obtained by warming the diacetate with concentrated sulphuric acid on the water-bath until the solution was bright blue and pouring it into water; the dione crystallised from pyridine in red laminæ, m. p. 254—256° (8·1 g., 55·8%). The analytical specimen was prepared by sublimation *in vacuo* at 220°, in dark red needles, m. p. 257—258° (Found: C, 65·0; H, 2·9; S, 10·6. Calc. for $C_{16}H_8O_4S$: C, 64·9; H, 2·7; S, 10·8%). The same product was obtained in only low yield from the anhydride (I), quinol, and zinc chloride at 185°, much unchanged anhydride being recovered. The brownish-yellow alkaline dithionite vat of the dione afforded, in air, a blue suspension, probably of the sodium salt of the dione. Reaction of the dione in pyridine with alcoholic potassium hydroxide gave a royal-blue precipitate, and deep royal-blue solutions resulted on interaction with primary aliphatic amines, but not aromatic amines.

7(or 10)-*Chloro*-6 : 11-*dihydro*-10(or 7)-*hydroxy*-6 : 11-*dioxobenzo*[b]*thiophanthrene.*—Replacement of quinol by *p*-chlorophenol (10 g.) in the above experiment gave yellow needles (from acetic anhydride) of the *acetoxy-diketone*, m. p. 249—250° (Found: C, 60·3; H, 2·5. $C_{18}H_9O_4ClS$ requires C, 60·6; H, 2·5%). This was warmed with concentrated sulphuric acid to give the *hydroxy-compound* (4·8 g., 31%), which sublimed *in vacuo* at 200°/3 mm. in orange-red needles, m. p. 260—261° (Found: C, 61·5; H, 2·3; Cl, 10·9; S, 10·2. $C_{16}H_7O_3ClS$ requires C, 61·0; H, 2·2; Cl, 11·3; S, 10·2%). It gave a reddish-blue solution in cold concentrated sulphuric acid.

6 : 11-*Dihydro*-7 : 10-*bismethylamino*-6 : 11-*dioxobenzo*[b]*thiophanthrene* (IV).—The dihydroxy-diketone (2 g.), sodium dithionite (2 g.), and 33% ethanolic methylamine (12 ml.) were heated in a sealed tube at 140—145° for 8 hr. The crude product was washed with warm water, dried (2 g.), extracted with toluene, and chromatographed on alumina, with toluene as eluant. 6 : 11-*Dihydro*-7 : 10-*bismethylamino*-6 : 11-*dioxobenzo*[b]*thiophanthrene* separated from impurities as an intense bluish-green band, eluted to a deep blue solution; crystallisation from toluene gave blue needles, m. p. 260° (1·44 g., 66·2%) (Found: C, 67·2; H, 4·6; N, 8·3; S, 10·2. $C_{18}H_{14}O_2N_2S$ requires C, 67·1; H, 4·4; N, 8·7; S, 10·0%). A small royal-blue band which

[7] Beyer and Richter, *Ber.*, 1940, **73**, 1325.

remained on the alumina column was extracted with acetic acid to give a blue solid, m. p. 170—184°, not investigated further.

7 : 10-*Bis*-n-*butylaminobenzo*[*b*]*thiophanthrene*-6 : 11-*dione* (IV).—The dihydroxy-diketone (2 g.), sodium dithionite (2 g.) and 33% ethanolic *n*-butylamine (14 ml.) were heated at 135—140° for 8 hr. The crude product was frequently obtained as a tar, and its acetone solution was dried (K_2CO_3); removal of acetone, followed by extraction with benzene and chromatography on alumina, gave a bluish-green band and thence bluish-violet needles (1·34 g., 49%). Crystallisation from light petroleum (b. p. 60—80°) gave the *bis*-n-*butylamino-derivative* as bluish-violet needles with a coppery lustre, m. p. 151° (Found : C, 71·0; H, 6·2; N, 6·8; S, 8·1. $C_{34}H_{36}O_2N_2S$ requires C, 70·9; H, 6·5; N, 6·9; S, 7·9%). A brown band remaining on the column was not examined.

1 : 4-*Bis*-n-*butylaminoanthraquinone*.—Recrystallised quinizarin (2 g.), sodium dithionite (2 g.), and 33% ethanolic *n*-butylamine (20 ml.) were heated at 140° for 8 hr. The product was dried in a vacuum, extracted with toluene, and purified by chromatography; toluene eluted a faint orange band (not examined), followed by the main intense blue band. Removal of solvent and crystallisation from light petroleum (b. p. 60—80°) afforded purple needles with a coppery lustre, m. p. 122°, of 1 : 4-*bis*-n-*butylaminoanthraquinone* (1·1 g., 38%) (Found : C, 75·2; H, 7·3; N, 8·4. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·5; N, 8·0%). This compound dyes cellulose acetate and Nylon a deep blue shade.

Condensation of the Anhydride (I) *with Resorcinol, to give a Fluorescein Analogue* (VI) *and* 3-(2 : 4-*Dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Acid* (V).—The anhydride (I) (8·2 g., 1 mol.) and resorcinol (8·8 g., 2 mols.) were melted together at 170° (internal temp.), and fused zinc chloride (3·4 g., 0·63 mol.) was added. After about 10 min., the mixture was too viscous to stir. It was then cooled to 90°, concentrated hydrochloric acid (2 ml.) in water (38 ml.) added, and the suspension boiled for 20 min. When cold, the plastic solid and crystals were filtered off. The plastic mass was dispersed to a yellow solid when ground with water; the total solid was then extracted with boiling 5% sodium carbonate solution (300 ml.) (charcoal) and the alkaline extract was filtered and acidified with hydrochloric acid; the resulting solid was dissolved in boiling acetic acid, and hot water added dropwise. First, the red granular fluorescein analogue was deposited; when the volume of the suspension was *ca.* 500 ml., the red solid was filtered off hot, and the filtrate allowed to cool, whereupon yellow needles separated. The *fluorescein analogue* (VI) was purified by repeating the above process and was a red granular solid, m. p. 287—289° (decomp.) (3·2 g., 20·5%) (Found : C, 68·4; H, 3·3; S, 8·5. $C_{23}H_{12}O_5S$ requires C, 68·0; H, 3·1; S, 8·3%). It is insoluble in ether, carbon tetrachloride, benzene, and *o*-dichlorobenzene, sparingly soluble in acetone and alcohols and moderately soluble in acetic acid. Its orange-red alkaline solution shows a strong green fluorescence. The above yellow needles of 3-(2 : 4-*dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic acid* (V) were crystallised several times from dilute acetic acid; they then had m. p. 254—255° (3·6 g., 28·6%) (Found : C, 61·3; H, 3·5; S, 10·6. $C_{16}H_{10}O_5S$ requires C, 61·1; H, 3·2; S, 10·2%). Although the yellow colour could not be removed by crystallisation from alcohol or acetic acid, a colourless sample was obtained by hydrolysis of the lactone (VIII) (see below). Aqueous-alcoholic solutions of the acid became reddish-brown on addition of ferric chloride solution. The acid is insoluble in carbon tetrachloride, sparingly soluble in benzene and cold water, soluble in *o*-dichlorobenzene and hot water, and very soluble in alcohols, acetone, ether, and acetic acid.

Interaction of the anhydride (I) (4·1 g., 1 mol.) and resorcinol (4·4 g., 2 mols.) at the temperatures shown (initial and final internal temperatures) gave the results tabulated.

Temp.	Time (min.)	Compound (VI) (g.)	Acid (V) (g.)	Temp.	Time (min.)	Compound (VI) (g.)	Acid (V) (g.)
150—155°	25	0·6	2·8	160—170°	25	1·3	2·0
150—155	40	0·5	2·4	165—175	25	1·7	2·2
150—160	15	1·8	1·9	180—195	5	1·6	1·9
160—167	15	0·8	1·5	210—225	1	2·6	1·3

Eosin Analogue (VII).—Excess of bromine (4·0 g.) was added slowly to the above red fluorescein analogue (2 g.) in absolute alcohol (10 ml.), and the mixture shaken for 1 hr.; the precipitate was filtered off and the *eosin analogue* (VII) crystallised from absolute alcohol in maroon needles, m. p. 295—297° (2·1 g., 57·8%) (Found : C, 37·7; H, 1·4; Br, 44·9; S, 4·7. $C_{23}H_8O_5Br_4S$ requires C, 37·5; H, 1·2; Br, 45·4; S, 4·6%).

3-(3 : 5-*Dibromo*-2 : 4-*dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Acid*.—3-(2 : 4-Dihydroxybenzoyl)thionaphthen-2-carboxylic acid (2 g.) in absolute alcohol (10 ml.) was treated with

bromine (4·0 g.), and the orange mixture shaken for 1 hr. The precipitated *dibromo-acid* was washed, and crystallised from acetic acid in orange prisms, m. p. 256—257°, containing 1 mol. of acetic acid of crystallisation (Found : C, 40·4; H, 2·1; Br, 30·2; S, 6·1. $C_{18}H_{12}O_7Br_2S$ requires C, 40·6; H, 2·3; Br, 30·0; S, 6·0%). The solvent was removed at 130° in 12 hr., with a change in colour from orange to a dull pink (2·2 g., 80·9%) (Found : C, 40·7; H, 2·1; Br, 34·0; S, 6·6. $C_{16}H_8O_5Br_2S$ requires C, 40·7; H, 1·7; Br, 33·9; S, 6·8%). Almost colourless specimens could be obtained by hydrolysing the lactone (XIV) (see below later).

3-(4-*Acetoxy*-2-*hydroxybenzoyl*)*thionaphthen*-2-*carboxylic Lactone* (VIII).—(a) *Use of acetyl chloride.* 3-(2 : 4-Dihydroxybenzoyl)thionaphthen-2-carboxylic acid (1·5 g., 1 mol.), xylene (50 ml.), and acetyl chloride (1·5 ml., 4 mols.) were refluxed for 12 hr. Yellow needles, m. p. 194—197°, were deposited on cooling. Recrystallisation from light petroleum (b. p. 60—80°)–benzene (1 : 1) afforded yellow needles, m. p. 199—200° (1·45 g., 90%) (Found : C, 63·7; H, 2·7; S, 9·6. $C_{18}H_{10}O_6S$ requires C, 63·9; H, 3·0; S, 9·5%), of the *lactone* (VIII). A small amount of crystals, insoluble in the light petroleum–benzene, was obtained unless larger quantities (4 ml.) of acetyl chloride were used. Crystallisation of this by-product from acetic acid yielded yellow needles, m. p. 289°, of the unacetylated lactone (XII).

(b) *Use of acetic anhydride.* The carboxylic acid (V) (1 g.) was refluxed with acetic anhydride (50 ml.) for 12 hr. and gave 91% (0·96 g.) of the lactone (VIII), m. p. and mixed m. p. 199—200°.

The acetylated lactone (VIII) was completely hydrolysed by refluxing 1% aqueous sodium hydroxide in 5 min., aqueous sodium hydrogen carbonate in 2 hr., or dilute hydrochloric acid (1 : 10) in 6 hr., to yield almost colourless needles, m. p. 254—255°, of 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid. When the lactone (VIII) was refluxed in distilled water for 18 hr., 43% was hydrolysed.

Methyl 3-(4-*Acetoxy*-2-*hydroxybenzoyl*)*thionaphthen*-2-*carboxylate* (XI).—The acetylated lactone (VIII) (1 g.) was refluxed with methyl alcohol for 12 hr. and, on cooling, colourless needles, m. p. 175—176°, of the *methyl ester* (XI) (0·95 g.) were obtained (Found : C, 61·6; H, 3·8; S, 9·0. $C_{19}H_{14}O_6S$ requires C, 61·6; H, 3·8; S, 8·7%).

3-(2 : 4-*Dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Lactone* (XII).—Freshly distilled thionyl chloride (1·4 g.) was refluxed with 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid (1·5 g.) in dry toluene (100 ml.) for 24 hr. On cooling, the crystals, m. p. 284—286°, were collected and recrystallised from acetic acid in bright yellow needles of the *lactone* (XII), m. p. 289° (decomp.) (1·32 g., 93·6%) (Found : C, 64·8; H, 2·3; S, 11·0. $C_{16}H_8O_4S$ requires C, 64·9; H, 2·7; S, 10·8%). Hydrolysis with boiling dilute aqueous sodium hydrogen carbonate afforded colourless needles, m. p. 254—255°, of 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid.

The lactone (XII) (0·5 g.), acetyl chloride (1 ml.), and toluene (80 ml.), refluxed for 13 hr., and then treated with light petroleum (b. p. 60—80°) (80 ml.) when cold, afforded yellow needles, m. p. 199—200°, of the acetylated lactone (VIII) (0·56 g., 98%).

Methyl 3-(2 : 4-*Dihydroxybenzoyl*)*thionaphthen*-2-*carboxylate* (XIII).—The lactone (XII) (1 g.) was refluxed in methyl alcohol (50 ml.) to give, after crystallisation from acetic acid, colourless plates, m. p. 206—207°, of the *methyl ester* (XIII) (1 g., 96%) (Found : C, 62·2; H, 3·8; S, 9·4. $C_{17}H_{12}O_5S$ requires C, 62·2; H, 3·7; S, 9·8%). It was also obtained by refluxing 3-(2 : 4-dihydroxybenzoyl)thionaphthen-2-carboxylic acid (1 g.) in methanol (100 ml.) saturated with hydrogen chloride, for 18 hr. (0·8 g., 77%).

Benzoylated Lactone of 3-(2 : 4-*Dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Acid.*—The carboxylic acid (1 g.) was refluxed with benzoyl chloride (1·4 g.) in toluene (60 ml.) for 10 hr.; an equal volume of light petroleum (b. p. 100—120°) was added; the *benzoylated lactone* separated; crystallisation from toluene–light petroleum gave pale yellow needles, m. p. 209—210° (1·1 g., 86%) (Found : C, 69·1; H, 2·9; S, 7·9. $C_{23}H_{12}O_5S$ requires C, 69·0; H, 3·0; S, 8·0%).

Acetylated Lactone of 3-(3 : 5-*Dibromo*-2 : 4-*dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Acid* (XIV).—(*a*) The carboxylic acid (1·5 g.) was refluxed with acetyl chloride (1 g.) in xylene (50 ml.) for 15 hr. Crystallisation of the product from benzene–light petroleum (b. p. 60—80°) afforded pale yellow needles of the *lactone* (XIV), m. p. 214—215° (1·47 g., 93%) (Found : C, 43·4; H, 1·3; Br, 32·1; S, 6·6. $C_{18}H_8O_6Br_2S$ requires C, 43·6; H, 1·6; Br, 32·2; S, 6·5%).

(*b*) The carboxylic acid (1 g.), refluxed with acetic anhydride (50 ml.) for 12 hr., yielded the lactone (XIV) (0·9 g., 85·6%). This lactone was readily hydrolysed by boiling aqueous sodium hydrogen carbonate to the colourless acid, which after heating at 130° gave m. p. and mixed m. p. with the pink sample obtained as above, 256—257° (Found : Br, 33·8; S, 6·8%).

3-(4-*Acetoxy*-3 : 5-*dibromo*-2-*hydroxybenzoyl*)*thionaphthen*-2-*carboxylic Acid* (XV).—The above

lactone (XIV) was crystallised from acetic acid containing a little water, to give colourless, hexagonal plates, m. p. 209—210°, of the *acid* (XV) (Found : C, 42·4; H, 2·2; Br, 31·0; S, 6·4. $C_{16}H_{10}O_6Br_2S$ requires C, 42·0; H, 2·0; Br, 31·1; S, 6·2%), soluble in aqueous sodium hydrogen carbonate with a yellow colour.

Methyl 3-(4-*Acetoxy*-3 : 5-*dibromo*-2-*hydroxybenzoyl*)*thionaphthen*-2-*carboxylate* (XVI).—The dibrominated acetyl lactone (XIV) (1 g.) was refluxed with methanol (60 ml.) for 12 hr., to give yellow plates, m. p. 194—195°, of the *methyl ester* (XVI) (1·96 g.) (Found : C, 42·7; H, 2·3; Br, 30·3; S, 6·4. $C_{19}H_{12}O_6Br_2S$ requires C, 43·2; H, 2·3; Br, 30·3; S, 6·1%).

3-(3 : 5-*Dibromo*-2 : 4-*dihydroxybenzoyl*)*thionaphthen*-2-*carboxylic Lactone* (XVII).—The carboxylic acid (1 g.) in chlorobenzene (100 ml.) was refluxed with thionyl chloride (1·5 ml.) for 6 hr. Buff-coloured needles were deposited; they crystallised from benzene containing a little light petroleum in yellow needles, m. p. 264—265° (0·72 g., 75%), of the *lactone* (XVII) (Found : Br, 35·3; S, 7·1. $C_{16}H_6O_4Br_2S$ requires Br, 35·2; S, 7·1%).

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291. *Organosilicon Compounds. Part XVII.* The Acidic Solvolysis of Organosilicon Hydrides.*

By J. E. BAINES and C. EABORN.

A kinetic study has been made of the decomposition of organosilicon hydrides by hydrogen chloride in aqueous ethanol or aqueous dioxan. It is concluded that the reaction involves nucleophilic attack by a solvent molecule on the silicon atom of the Si–H bond and electrophilic attack by an oxonium ion on the hydrogen atom.

There is a linear relation over the whole range of acid concentrations between the logarithm of the velocity constant for a given organosilane and the logarithm of the ratio of conjugate acid to free base for *p*-nitroaniline.

TAKETA, KUMADA, and TARAMA [1] concluded that the rate of acidic ethanolysis of triethylsilane is proportional to the square of the mean activity of hydrogen chloride, and thus to the product of the activities of chloride and oxonium ion. The implication of this, either that both chloride ion and oxonium ion are involved in the rate-determining step, or that catalysis is by undissociated hydrogen chloride, seemed to us improbable, and our view is confirmed by the work described below.

Dependence of Rate on Acid Concentration.—To avoid difficulties with traces of water which are formed in solutions of strong acids in ethanol, we used aqueous 95% ethanol as solvent, and to facilitate measurements in dilute acid we used the reactive di-*n*-propyl- and *cyclo*hexyl-silane.

The acidic solvolysis of di-*n*-propylsilane takes place stepwise. The first Si–H bond is broken some 18 times as quickly as the second, and first-order rate constants, k_1 and k_1', for the two steps may be obtained from a single run, but only k_1 is of interest. (The rate constant k_1' probably refers to the hydrogen evolution from *s*-tetra-*n*-propyldisiloxan.)

Table 1 shows that below 0·5M-acid, k_1 is accurately proportional to the hydrogen chloride concentration, and thus to the concentration of oxonium ion, since dissociation is complete in this medium.[2] (In agreement with this, the rates are not significantly different when perchloric acid is used.) At higher concentrations k_1 increases more rapidly with acid concentration, the variation in the range 0·6—1·4M being expressed roughly by the equation $10^4k_1 = 87[HCl] + 68[HCl]^2$.

* Part XVI, *J.*, 1955, 4023.

[1] Taketa, Kumada, and Tarama, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1953, **31**, 260.

[2] Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330.

Table 1 also shows that there is an exact linear relation between log k_1 and log I, where I is the indicator ratio (at 18°) for *p*-nitroaniline (*i.e.*, the ratio of the concentration of the conjugate acid of *p*-nitroaniline to that of the free base). This linearity covers the whole range of acid concentration, and not just the lower part in which both log k_1 and log I are proportional to log [HCl].

TABLE 1. *Solvolysis of di-*n*-propylsilane in aqueous-ethanolic hydrogen chloride at* 34·9°.

[HCl] (M)	0·109	0·195	0·390	0·651	0·977	1·302	1·954
10^2k_1 (min.$^{-1}$)	1·31	2·43	4·94	8·57	14·4	22·2	48·8
I	0·035(4)	0·104	0·314	0·782	1·795	3·796	12·17
10^2k_1/[HCl]	12·0	12·5	12·7	13·2	14·8	17·1	25·0
$-$ (log k_1 $-$ 0·62 log I)	1·98	2·00	2·00	2·00	2·00	2·01	1·98

The range of low acid concentration was investigated more accurately with *cyclo*hexylsilane. The initial rate of hydrogen evolution was used as a measure of the rate of reaction and could be determined with accuracy because it remained constant during the evolution of 20% of the hydrogen available. (The apparent zero-order nature of the hydrogen evolution must result from similar reactivites of all three available hydrogen atoms in the stepwise decomposition. The initial rate is, in fact, proportional to the initial concentration of the organosilane.) Again (Table 2), the rate of reaction (expressed as a zero-order rate constant, k_0, which is the rate of hydrogen evolution arbitrarily divided by the volume of hydrogen which would be obtained from complete reaction of one Si–H bond of the *cyclo*hexylsilane), is proportional to the acid concentration below 0·6M. Above this the variation in rate has the same form as that for di-*n*-propylsilane, log k–[HCl] plots for the two hydrides being superimposable. It follows that log k_0–log I plots for *cyclo*hexylsilane are linear, as confirmed by the constancy of (log k_0–0·6 log I) in Table 2.

TABLE 2. *Solvolysis of* cyclo*hexylsilane in aqueous-ethanolic hydrogen chloride at* 34·9°.

[HCl] (M)	0·0245	0·049	0·098	0·131	0·163	0·196	0·327	0·490	0·654	0·980	1·300
10^2k_0 (min.$^{-1}$)	0·125	0·257	0·513	0·677	0·835	0·996	1·68	2·56	3·53	5·61	8·52
$10k_0$/[HCl]	0·51	0·52	0·52	0·52	0·51	0·51	0·51	0·52	0·54	0·57	0·66
I *	—	—	0·030	0·051	0·075	0·105	0·232	0·460	0·784	1·802	3·79
$-$ (log k_0 $-$0·6 log I)	—	—	1·38	1·40	1·40	1·41	1·39	1·39	1·39	1·40	1·42

* Obtained by interpolation from experimental values in Table 1.

It appears that the form of dependence of rate on acid concentration is not much influenced by the organosilicon hydride employed, and similar results would be expected for triethylsilane. It is thus interesting to re-examine Taketa, Kumada, and Tarama's data [1] for its reaction in anhydrous ethanolic hydrogen chloride, and the variation in $k_1/([\mathrm{HCl}] \times f)^2$ (where f is the activity coefficient of hydrogen chloride) shows (Table 3)

TABLE 3. *Reaction of triethylsilane with ethanolic hydrogen chloride at* 50°. (Kinetic data from Taketa, Kumada, and Tarama.[1])

[HCl] (M)	0·0425	0·085	0·127	0·170	0·525	1·05	1·57	2·10
10^2k_1 (min.$^{-1}$)	0·06	0·158	0·255	0·362	1·12	3·74	7·70	13·30
$k_1/([\mathrm{HCl}] \times f)^2$	2·30	2·28	2·01	1·72	1·25	1·54	1·59	1·78
10^2k_1/[HCl]	(1·42)	1·86	2·02	2·13	2·13	—	—	—
I	0·88	1·81	2·72	3·65	8·50	22·42	—	—
$-$ (log k_1 $-$1·27 log I)	4·15	4·13	4·14	4·15	4·15	4·15	—	—

that the rate is not proportional to the activity of hydrogen chloride as they claim. A k_1–[HCl] plot is a straight line for the four lowest acid concentrations, but does not pass through the origin, and we suggest that the rate is in fact proportional to the acid concentration but that there is a small constant experimental error in k_1 (possibly associated with the "induction period"). This will be most serious for the weakest acid, and if the figure for this is neglected, k_1/[HCl] is reasonably constant up to 0·525M-acid. Further,

over the whole range of concentration for which values of I may be obtained by interpolation from Braude's data,[3] values of (log k_1 $-1{\cdot}27$ log I) are reasonably constant.

Addition of Water and Salts.—Increase in the water content of the medium from 5% to 10% causes a decrease in the rate of reaction, this decrease being relatively greater the higher the concentration of acid, as revealed in Table 4, which refers to the reaction of di-*n*-propylsilane at 34·9°.

TABLE 4.

[HCl] (M)	1·954	1·302	0·977
10^3k_1 (min.$^{-1}$) (in 95% EtOH)	48·8	22·2	14·4
10^3k_1 (min.$^{-1}$) (in 90% EtOH)	31·0	18·0	12·7

Inhibition by added water is common for acid-catalysed reactions in alcoholic solvents,[4] and is associated with the replacement of ethoxonium ions by the less reactive hydroxonium ions. The increase in the effect as the acid concentration is raised may reasonably be related to the greater lowering of log I by added water at higher acid concentrations.[4]

As shown in Table 5 (which refers to the reaction of di-*n*-propylsilane in 95% ethanol at 34·9°) additions of lithium chloride or tetraethylammonium bromide increase the rate of reaction (but the former rather less than would be expected if the equation 10^4k_1 = 87[HCl] + 68[H^+][Cl^-] applied). In view of the low dielectric constant of the medium, which magnifies salt effects, there is no reason to doubt that the rate changes are purely medium effects, chloride or bromide ions not entering into the reaction. Though both salts raise the reaction rate, the lithium salt raises the value of log I while the tetraethylammonium salt lowers it, probably because both salts raise the activity coefficient of the organosilane while the former raises, and the latter lowers, the activity coefficient of *p*-nitroaniline.[5]

TABLE 5.

[HCl] (M)	0·977	0·977	0·977	0·977	0·710	0·710	0·710	0·710
Salt	—	LiCl	LiCl	LiCl	—	Et_4NBr	Et_4NBr	Et_4NBr
[Salt] (M)	—	0·263	0·469	0·960	—	0·129	0·285	0·479
10^3k_1 (min.$^{-1}$)	1·37	1·45	1·56	1·90	0·98	1·00	1·03	1·11
log I	0·27	0·29	0·43	—	−0·04	−0·06	−0·08	−0·13

Solvent Isotope Effect.—The reaction of *cyclo*hexylsilane is 2·25 times as fast in protium oxide–dioxan as in deuterium oxide–dioxan, as shown in Table 6 which refers to 0·490M-hydrogen chloride at 34·9°.

TABLE 6.

	Protium oxide				Deuterium oxide	
Vol. % of H_2O (or D_2O)	0	10	20	20	20	20
k_0 (min.$^{-1}$)	<0·0002	0·0089	0·0133	0·0134	0·0059(3)	0·0058(9)

This means that proton transfer occurs in the rate-determining step and not in a prior fast reversible step. The assumption involved, *viz.*, that acids are more dissociated in protium oxide–dioxan than in deuterium oxide–dioxan, has been experimentally justified in the case of the conjugate acid of *p*-nitroaniline (unpublished work by Mr. J. B. Hurd).

Variation of Structure.—The rate constants at two temperatures for several triorganomonosilanes, R_3SiH, at the same hydrogen chloride concentration (1·430M) in 95% ethanol are shown in Table 7 along with approximate activation energies, E (the variations in which are not significant). All the reactions were of first order in organosilane.

The effects of *para*-substitution show that electron release to silicon slightly hinders the reaction. The low reactivity of tri*iso*propylsilane compared with that of the normal compound (relative reactivities, 1 : 10) is probably mainly a steric effect, comparable with that in alkaline hydrolysis in which the reactivity ratio is 1 : 20 but in which electron release by the *iso*propyl group contributes more to the inhibition.

[3] Braude, *J.*, 1948, 1971.
[4] Braude and Stern, *J.*, 1948, 1976.
[5] Long and McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3243.

TABLE 7.

R_3 in R_3SiH	Et_3	Pr^n_3	Bu^n_3	Bu^i_3	Pr^i_3	Ph_3
10^3k_1 (34·9°)	1·19	0·745	0·70	0·20	0·07	0·40
10^3k_1 (45·0°)	3·03	2·07	1·95	—	—	—
E, kcal./mole	18·1	19·8	19·9	—	—	—
Relative rates (34·9°) *	1	0·63	0·59	0·17	0·06	0·3

R_3 in R_3SiH	$(p\text{-}C_6H_4Cl)_3$	$(p\text{-}C_6H_4Cl)Me_2$	$PhMe_2$	$(p\text{-}C_6H_4Me)Me_2$
10^3k_1 (34·9°)	1·5	2·58	2·13	1·82
10^3k_1 (45·0°)	—	—	5·52	5·02
E, kcal./mole	—	—	18·5	19·7
Relative rates (34·9°) *	1·3	2·2	1·8	1·5

* At this acid concentration, the relative reactivities of $C_6H_{11}SiH_3$, $Pr^n_2SiH_2$ (first Si-H), and Et_3SiH are 120 : 22 : 1.

The variation in reactivity of the organosilicon hydrides examined is small compared with that in other reactions.[6, 7]

Mechanism of the Reaction.—The observed solvent isotope effect and the first-order dependence of rate on acid concentration in dilute acid mean that electrophilic attack by an oxonium ion on the hydrogen atom of an Si–H bond is involved in the rate-determining step. However, since the reaction is hindered by electron-release to the silicon atom, the latter must be more negatively charged in the transition state than in the ground state, and thus there must also be nucleophilic attack on silicon, normally by a solvent molecule. In agreement with this, reaction is very slow in anhydrous dioxan (although the proton-availability, as measured by I, is quite high [3]); a much faster reaction occurs when water is added, and the rate increases with the water concentration even though the value of I falls.[4]

Since in alkaline hydrolysis, in which electrophilic attack on the incipient hydride ion of the Si–H bond is by a water molecule, $SiH \cdots HOH$ bonding is considerable in the transition state,[8] the analogous $SiH \cdots \overset{+}{H}OH_2$ bonding should be even stronger in acid catalysis when attack is by the positively charged oxonium ion. This explains the relatively small solvent isotope effect, since the loss of zero-point energy from the $H\text{–}{}^+OH_2$ bond is partially compensated by the gain in zero-point energy in the $H \cdots H$ bond of the transition state.

A two-stage mechanism fits the facts, the first step being fast and reversible and the second rate-determining:

$$\equiv SiH + H_2O \rightleftharpoons H_2\overset{+}{O}\text{–}\underset{|||}{\overset{-}{S}}iH \; ; \; H_2\overset{+}{O}\text{–}\underset{|||}{\overset{-}{S}}iH + H\text{–}\overset{+}{O}H_2 \longrightarrow H_2\overset{+}{O}Si\equiv + H_2 + H_2O$$

(There will be a subsequent fast proton loss from $\equiv Si\overset{+}{O}H_2$.) In the rate-determining transition state the silicon atom is more negative than in the (original) ground state even if the Si–H bond is considerably stretched. The transition state could be reached without formation of an intermediate, in a synchronous process in which the new bond to silicon is slightly more formed than the Si–H is broken, but this would involve a termolecular collision.

Since the rapid increase in rate in more concentrated acids is paralleled by increase in the indicator ratio, I, it is reasonable to attribute it to a medium effect rather than to a change in mechanism, but the possibility of intervention by chloride ion or undissociated hydrogen chloride has not been experimentally excluded. Since dissociation is substantially complete in the solvent used, undissociated hydrogen chloride would need to be very reactive for its intervention to cause the rate increase.

Acidity Functions in Organic Solvents.—Braude [3] first measured the indicator ratios for solutions of *p*-nitroaniline in anhydrous or aqueous ethanol, acetone, or dioxan, and derived acidity functions H, by means of the relation $H = \log I - \log K_B^{H,O}$ which holds in aqueous solutions ($K_B^{H,O}$ being the indicator constant in dilute aqueous solution). Gutbezahl and Grunwald [9] point out, however, that values of f_{BH^+}/f_B (which determine I for a given base,

[6] Baines and Eaborn, *J.*, 1955, **4023**.
[7] (*a*) Deans and Eaborn, *J.*, 1954, **3169**; (*b*) Eaborn, *J.*, 1955, 2517.
[8] Kaplan and Wilzbach, *J. Amer. Chem. Soc.*, 1955, **77**, 1297.
[9] Gutbezahl and Grunwald, *ibid.*, 1953, **75**, 559.

and hence H), where f_B is the activity coefficient of the neutral base and f_{BH^+} that of its conjugate acid, are not independent of the base in solutions of low dielectric constant, and thus the acidity function concept has no application in alcoholic solvents.

Use of acidity functions for a given solvent containing varying amounts of acid would be empirically justified by a unit-slope straight-line plot of log I for one base against log I' for another base, but in 27% water in methanol, for example, the log I–log I' plot even for the related bases *p*- and *o*-nitroaniline, while it is a straight line, has a slope of 0·82 (unpublished work by Mr. J. B. Hurd). It follows that the unit slope of the log k–H plot in acidic cleavage of *p*-methoxyphenyltrimethylsilane in this solvent [10] is fortuitous, depending on the choice of *p*-nitroaniline as indicator.

The significance of the linearity of log k–log I and log I–log I' plots is not clear; either non-linearity or unit-slope linearity would be expected. Slopes of up to 1·4 for straight-line log k–H plots in aqueous solutions have been explained as salt effects, log k–(H − constant × c_A) plots (c_A is the concentration of acid) being unit-slope straight lines, but no such plot fits our data. [Plots of log k–log I and log k–(log I − constant × c_A) can both be linear only if log I is proportional to c_A, and this is not even approximately true in 95% ethanol.]

It is tempting to infer that when log k–log I relations are of the same type as log I–log I' relations, then the transition state of the reaction is the conjugate acid of the ground-state molecule, but in the acidic solvolysis of organosilyl hydrides the transition complex also contains solvent molecules. Perhaps the only reasonable inference, and this tentative, is that variations in k with acid concentration (outside those expected for simple proportionality) are caused by the medium effects which account for the variations in I, and not by mechanistic changes.

Experimental

Materials.—p-*Chlorophenyldimethylsilane*, b. p. 199·5°, n_D^{20} 1·5188 (Found: C, 56·6; H, 6·7. $C_8H_{11}ClSi$ requires C, 56·3; H, 6·5%), was prepared by treating trichlorosilane (1 mol.) successively with *p*-chlorophenylmagnesium bromide (1 mol.) and methylmagnesium iodide (2 mol.) in ether. To remove a fuming impurity the product was dissolved in methanol and recovered after ½ hr.

Dimethyl-p-tolylsilane, b. p. 181—182°, n_D^{20} 1·5000 (Found: C, 71·7; H, 9·2. $C_9H_{14}Si$ requires C, 71·9; H, 9·4%), was prepared by reduction of fluorodimethyl-*p*-tolylsilane with excess of lithium aluminium hydride. The product was free from unchanged fluoride.

Rate Measurements.—Reactions were carried out in the twin-limbed vessels previously described,[7 (b)] supersaturation and the apparent induction period [1] thus being avoided.

(i) *With aqueous-ethanolic hydrochloric acid.* The "95% ethanol" was a water–ethanol mixture of *s.g.* 0·8161 at 60° F (5 vol.-% of water), and dry hydrogen chloride was dissolved in it as required. Usually 5 ml. of a *ca.* 0·20M-solution of the organosilane were mixed with 10 ml. of the acid solution, but because of limited solubilities larger volumes of more dilute solutions were used for triarylsilanes.

The following typical runs illustrate procedures. The volumes of hydrogen, V_t, were measured over water at the temperature and pressure given in parentheses, and the infinity values, V_∞, are the theoretical volumes expected.

(*a*) Et_2SiH (initially) 0·0673M, [HCl] 1·430M; 34·9°.

Time (t) (min.)	0	29	64	94	129	169	236	292	389	449	∞
V_t (ml., 20°, 747 mm.)	0	0·83	1·91	2·63	3·75	4·77	6·33	7·50	9·52	10·57	25·30
10^3k_1 * (min.$^{-1}$)	—	1·15	1·22	1·16	1·25	1·24	1·22	1·20	1·21	1·21	—

* $k_1t = \ln[V_\infty/(V_\infty - V_t)]$.

(*b*) $Pr^n{}_2SiH_2$ (initially) 0·0337M, [HCl] 1·430M; 34·9°.

Time (t) (min.)	0	3	5	10	18	23	28	60	226	299	343	403	486	∞
V_t (ml., 20°, 758 mm.)	0	0·94	1·52	2·84	4·56	5·55	6·44	10·29	15·76	16·76	17·28	17·88	18·62	24·82
10^3k_1 * (min.$^{-1}$)	—	26·3	26·1	26·0	25·4	25·8	26·1	—	—	—	—	—	—	—
$10^3k_1'$ * (min.$^{-1}$)	—	—	—	—	—	—	—	—	1·42	1·44	1·42	1·44	1·44	—

* $k_1t = \ln[12·42/(12·42 - V_t)]$; $k_1't = \ln[12·42/(24·84 - V_t)]$, it being assumed that after 226 min. only the second Si–H bond is reacting.

[10] Eaborn, *J.*, 1953, 3148.

(*c*) $C_6H_{11}SiH_3$ (initially) 0·0663M, [HCl] 0·980M; 34·9°.

Time (*t*) (min.) ...	0	1	2	3	4	5	6	7	8	9	10	13·5	∞
V_t (ml., 21°, 759 mm.)	—	1·38	2·78	4·14	5·50	6·68	8·26	9·62	10·94	12·23	13·48	17·60	73·8
V_t/t (min.$^{-1}$)	—	1·38	1·39	1·38	1·38	1·37	1·38	1·37	1·37	1·36	1·35	1·30	—

$$k_0 = 3V_t/tV_\infty = 0{\cdot}0557 \text{ min.}^{-1}.$$

(ii) *Aqueous-ethanolic perchloric acid.* The acid solution was made by mixing 5 ml. of aqueous acid with 95 ml. of ethanol. The reaction mixture thus contains slightly less than 5 vol.-% of H_2O but this is unimportant at the acid concentrations involved (see Table 4). The rate constants in parentheses are those for corresponding concentrations of hydrochloric acid.

$[HClO_4]$ (M)	0·374	0·311	0·272
10^3k_1 (min.$^{-1}$)	4·90 (4·7)	4·05 (3·9)	3·50 (3·4)

(iii) *In aqueous dioxan.* The silane in dioxan (5 ml.) was added to 3 ml. of a 1·633M-solution of hydrogen chloride in dioxan (purified,[11] and dried by prolonged boiling with sodium) either with 2 ml. of water or with 1 ml. of water and 1 ml. of dioxan. Deuterium oxide was the 99·8% material.

Indicator Ratios.—These were measured in 95% ethanol by standard spectrophotometric techniques and the symbols below have the usual meaning.[9, 10] The values of λ_B and ε_B are 378 and 15,425 respectively.

10^3 [HCl] (M)	109	195	390	651	977	1302	1954
λ_A (mμ)	378	378	378	378	378	375	371
ε_S	47	47	48	48	48	57	73
ε_A	14,900	13,975	11,750	8675	5550	3260	1290
10^3I	35·(4)	104	314	782	1795	3796	12,170

We thank Imperial Chemical Industries Limited for a grant for chemicals, and the Nobel Division of that Company for a maintenance award to one of us (J. E. B.).

UNIVERSITY COLLEGE, LEICESTER. [*Received, November 16th*, 1955.]

[11] Eigenberger, *J. prakt. Chem.*, 1931, **130**, 75.

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292. *Electrophilic Substitution. Part II.* The Nitration of Naphthalene and Perylene.*

By M. J. S. DEWAR and T. MOLE.

Naphthalene and perylene have been nitrated with nitric acid in acetic anhydride. The proportions of α- and β-nitronaphthalene have been obtained spectrophotometrically. It has been established that mononitration of perylene yields very largely one isomer, which is believed to be 3-nitroperylene. Aminoperylene has been prepared by reduction of the nitro-compound.

FIERZ-DAVID and SPONAGEL[1] nitrated naphthalene in sulphuric acid and in a mixture of acetic acid and acetic anhydride. By comparing the melting points of the mixtures of mononitronaphthalenes formed with those of synthetic mixtures of the α- and the β-isomer they calculated the ratio of the isomers as α/β = 17·2. This value compares well with the value, 17·87, quoted by Fedorow and Spryskow[2] on the basis of spectrophotometric studies. Bavin[3] nitrated naphthalene in acetic anhydride, and, using the analytical method of Fierz-David and Sponagel, he deduced that α/β = 15·1. The method is, however, not accurate; further, the earlier workers, except Bavin, did not use exclusively mononitrating media. The ultraviolet spectra of α- and β-nitronaphthalene differ

* Part I, *J.*, 1956, 164.

[1] Fierz-David and Sponagel, *Helv. Chim. Acta*, 1943, **26**, 98.
[2] Fedorow and Spryskow, *Chem. Zentr.*, 1935, I, 1423; II, 90; *Z. analyt. Chem.*, 1935, **101**, 188.
[3] Bavin, Thesis, London, 1955; *Anilinokrassotschaja Promyschlennost*, 1934, **4**, 103, 627.

appreciably, and it should be possible to determine spectrophotometrically the percentage of the β-isomer in a mixture of the two isomers to within $\pm\frac{1}{2}\%$.

We have nitrated naphthalene with nitric acid in acetic anhydride at 0°, 20°, and 45°, using an excess of the hydrocarbon. Chromatography on alumina was used to free the mixed mononitronaphthalenes from excess of naphthalene and from the small amount of quinones formed (<2% of the naphthalene which reacted). The ratio α : β was determined by comparing the ultraviolet spectra of the mixtures with the spectra of the pure isomers.

Pure α-nitronaphthalene was obtained by recrystallisation and chromatography of commercial α-nitronaphthalene. β-Nitronaphthalene was synthesised from β-naphthylamine *via* the diazonium fluoroborate and was purified in the same way as the α-isomer. Spectra were measured in ethanol solutions, of total nitronaphthalene concentration 20 mg./l. ($1{\cdot}155 \times 10^{-4}$M), over the range 240—380 mμ, with a Unicam S.P. 500 spectrophotometer. Under these conditions the spectra of synthetic mixtures were reproducible and were additive functions of the percentages of α- and β-isomers. With more dilute solutions (2×10^{-5}M) in ethanol, and with solutions in *cyclo*hexane, these spectra were not readily reproducible and did not always obey Beer's law. Specimen results are quoted in Table 1.

TABLE 1. *Molar extinction coefficients* ($\times 10^{-3}$) *measured in* $1{\cdot}155 \times 10^{-4}$M-*solutions in ethanol.*

λ (mμ)	α	β	α + β at 0°	α + β at 20°	α + β at 45°
330	4·1	2·3	4·0	4·0	4·0
300	2·4	8·2	2·9	2·9	3·1
260	5·9	23·2	7·6	7·5	7·9
250	8·2	19·6	9·3	9·2	9·5

Our measurements have led us to conclude that, for the nitrations at 0° and 20°, $\alpha/\beta = 10$; for the nitration at 45° the ratio is somewhat lower (see Table 2).

TABLE 2.

Temperature	0°	20°	45°
β-Isomer (%)	9—10	8·5—9·5	11—12
Ratio, α : β	10 : 1	10 : 1	8 : 1

Examples of the monosubstitution of perylene are rare,[4] but the hydrocarbon readily undergoes polysubstitution. Di- and tetra-nitration have already been described;[5] in tetranitroperylene[6] the nitro-groups occupy positions 3, 4, 9, and 10. Mononitration must therefore occur in the 3-position.

(I)

Perylene has now been mononitrated in acetic anhydride solution, with an excess of hydrocarbon present. The product was chromatographed on alumina to free the nitro-compounds from residual hydrocarbon and a small quantity of quinone by-product. At least 94% of the nitro-compounds formed was shown to consist of a single isomer of m. p. 210—211°, and no other isomer could be isolated.

3-Nitroperylene was rapidly reduced to the corresponding amine with hydrazine hydrate in ethanol in the presence of palladised charcoal, the yield being good. We believe this to be the first recorded instance of the use of palladised charcoal to catalyse the reduction of aromatic nitro-compounds by hydrazine hydrate.

EXPERIMENTAL

Pure α-nitronaphthalene was obtained as yellow needles, m. p. 57·3—58·3°, by recrystallising commercial α-nitronaphthalene twice from alcohol and chromatographing this product on alumina from benzene–light petroleum.

[4] Zinke, Troger, and Ziegler, *Ber.*, 1940, **73**, 1042.
[5] Zinke and Unterkreuter, *Monatsh.*, 1919, **40**, 405; Zinke, Funke, and Lorber, *Ber.*, 1927, **60**, 580.
[6] Zinke, Hirsch, and Brozek, *Monatsh.*, 1929, **51**, 205.

Naphthalene-2-diazonium fluoroborate, prepared from β-naphthylamine,[7] was converted into β-nitronaphthalene by the method of Hodgson and Marsden;[8] the crude nitro-compound was purified in the same way as α-nitronaphthalene, giving pale yellow needles, m. p. 77·5—78·2°.

Nitration of Naphthalene.—Nitric acid (0·8 ml.; *d* 1·5) in ice-cold acetic anhydride (5 ml.) was slowly added to a stirred solution of naphthalene (B.D.H. microanalytical standard; 4·00 g.) in acetic anhydride (200 ml.) at 0°; the solution was kept at 0° for 2 days. In other experiments nitration was at 20° and 45°.

The acetic anhydride was hydrolysed in excess of water and the product was extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed in light petroleum four times on 20 × 4 cm. columns of alumina (Peter Spence, type " H "). In each case as much naphthalene as possible was removed by elution with light petroleum, and the nitronaphthalene band was then eluted with ether. Some quinone (<10 mg.) was left on the columns.

Temperature	0°	20°	45°
$C_{10}H_7{\cdot}NO_2$ (g.)	2·12	2·84	3·04
Yield, % with respect to HNO_3	68	92	99

Perylene.—Perylenetetracarboxylic acid dianhydride, prepared from dinaphthalimide,[9] was decarboxylated by heating to 400—500° with soda-lime; the hydrocarbon was sublimed and recrystallised from α-methylnaphthalene–light petroleum (b. p. 100—120°), giving golden-yellow plates (50%), m. p. 271—272°.

Nitration of Perylene.—Nitric acid (0·2 ml.; *d* 1·5) in ice-cold acetic anhydride (20 ml.) was slowly added to a stirred solution of perylene (1·04 g.) in acetic anhydride (1·5 l.) at 15°. After 24 hr. the anhydride was hydrolysed in excess of water, and the product was extracted with chloroform (1 l.). The extract was washed with sodium hydrogen carbonate solution and the chloroform was distilled off; the residue was chromatographed in benzene on a 20 × 4 cm. column of alumina (Peter Spence, type " H "). The yellow perylene band was eluted with light petroleum–benzene (1 : 1), and the nitroperylene was then removed with benzene–alcohol (4 : 1). The nitroperylene was rechromatographed; the column was eluted with benzene–light petroleum, then with benzene, and finally with benzene–alcohol (10 : 1). Several fractions were taken and recrystallised; the mother-liquors were combined and rechromatographed, and fractions were again taken. Only one isomer was found, the brick-red, crystalline *3-nitroperylene*, m. p. 210—211° (Found: C, 80·2; H, 3·9; N, 4·6. $C_{20}H_{11}O_2N$ requires C, 80·8; H, 3·7; N, 4·7%). Light absorption max. in EtOH at 295, 347, 459 mμ ($\log_{10}\varepsilon$ 3·60, 3·57, 4·66). Of 494 mg. of nitroperylene isolated, 467 mg. (94%) were identified by m. p. with this isomer.

Reduction of 3-Nitroperylene.—Hydrazine hydrate (1 ml.) and 5% palladium–charcoal (20—50 mg.) were added to nitroperylene (50 mg.) in boiling alcohol (50 ml.). After 10 min. the solution had become bright yellow; it was filtered and the alcohol distilled off. The residue crystallised from benzene as yellow-brown plates of *3-aminoperylene*, m. p. 220—230° (decomp.) (30 mg.) (Found: C, 89·3; H, 5·1; N, 5·3. $C_{20}H_{13}N$ requires C, 89·8; H, 4·9; N, 5·3%). Light absorption max. in EtOH at 261, 325, 462 mμ ($\log_{10}\varepsilon$ 4·44, 3·66, 4·30).

We thank Imperial Chemical Industries Limited, Dyestuffs Division, for a gift of dinaphthalimide, and the University of London for a grant for the purchase of a spectrophotometer. One of us (T. M.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

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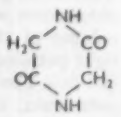
[7] *Org. Reactions*, **5**, 193.
[8] Hodgson and Marsden, *J.*, 1944, 22.
[9] G.P. 394,794/1921.

293. *Glycine Peptides. Part II.* The Heat and Entropy of Formation of the Peptide Bond in Polyglycine.*

By A. B. Meggy.

Piperazine-2 : 5-dione polymerises to polyglycine in the presence of a limited amount of water, at 60—180°. The reaction at 140° has been studied in detail, and from a comparison with the results at 180° it is concluded that both the heat and the entropy of the reaction are small. From the degree of polymerisation of polymers obtained over the range 120—180°, the heat and the entropy of formation of the peptide bond in solid polyglycine have been calculated as 3·3 kcal. mole^{-1} and 17 cal. mole^{-1} degree^{-1}, respectively. Glycine polymerises to polyglycine at temperatures above 140°, in the presence of water, and of solid glycine. From the partial pressure of water in the system, it is calculated that for this reaction ΔH = 3·3 kcal. mole^{-1}, and ΔS = 5·9 cal. mole.$^{-1}$ degree^{-1}. On the assumption that the values are similar for the formation of peptide bonds from other amino-acids, synthesis of proteins under biological conditions is possible thermodynamically if the formation of the peptide bond is coupled with the hydrolysis of adenosine triphosphate, pyrophosphate, or polyphosphate.

It has been shown[1] that heating piperazine-2 : 5-dione (I) with water at 180° yields a polymer of glycine. The reaction has now been studied at temperatures down to 60°. At 140° the reaction is complete in about two days, and at 120° in about three weeks; at 100° the reaction was incomplete after 14 weeks, and at 60° some polymer had been formed after three months. At 40° there was no sign of polymerisation after two years. The small amount of polymer formed at 60° was partially soluble in boiling water; the insoluble portion was identified as polyglycine by its *X*-ray diffraction pattern.



(I)

The reaction was studied in detail at 140°, the irreversible decomposition to ammonium carbonate and other products, which takes place at 180°, being then inappreciable. The results are summarised in Tables 1 and 2. The analytical methods are described in Part I. Table 1*a* shows the course of the reaction when the ratio of water to dione is 1 : 1 by weight. Column 2 gives the percentage of dione converted into insoluble

Table 1.

Time (hr.)	Percentage of total N as polymer	$-NH_2$	dione	peptide	NH_3 or $(NH_4)_2CO_3$	Mean D.P. of sol. peptides
1	2	3	4	5	6	7
			a. Dione : water = 1 : 1 (w/w).			
7	2·5	3·4	83	5·5	—	1·62
19	60	21·5	20·9	20·3	2·0	0·95
24	65	18·8	17·9	17·9	1·6	0·95
42	60·5	23·8	10·9	27·6	1·8	1·18
114	50	33·8	7·3	35·9	5·9	1·06
			b. 10% of dione replaced by glycylglycine.			
7	39·5	9·5	40·2	17·5	—	1·84
17	55·5	13·2	22·0	25	—	1·90
30	56·5	16·9	15·8	27·3	0·9	1·62
51	60·5	22·7	10·8	26·8	1·3	1·18

polymer, which for all practical purposes is equal to the percentage of dione-nitrogen present as polymer-nitrogen. Columns 3, 4, and 5 refer to the aqueous phase. The degrees of polymerisation recorded in column 7 are obtained by dividing the figures in column 5 by those in column 3, and so refer to the soluble peptides. It is apparent from column 7 that from 19 hours onwards the aqueous phase contains only piperazine-2 : 5-dione, glycine, and a small

* Part I, *J.*, 1953, 851.

[1] Meggy, *J.*, 1953, 851.

amount of ammonia (or its carbonate), higher peptides being almost completely absent. (The minimum real value for column 7 is 1; the value of 0·95 arises from accumulating errors in the analytical methods.)

Table 1*b* shows the result of replacing 10% of the dione by glycylglycine. The initial stages of the reaction are greatly accelerated; after 7 hours there is about 40% polymer formation, compared with 2·5% without glycylglycine. However, the degree of polymerisation of the soluble peptides is between 1·5 and 2 for the first 30 hours, showing that glycylglycine is being formed by the hydrolysis of dione as quickly as it is being consumed in the formation of polymer. A similar catalytic effect is shown by small amounts of acids and bases. The results suggest that the first stage in the reaction is the hydrolysis of dione to glycylglycine, this being followed by the addition of dione molecules to the peptide. The later stages of the catalysed and the uncatalysed reaction are the same. Glycine and alanine also catalyse the reaction, though less effectively; however, when a polymer prepared with alanine as catalyst was hydrolysed with acid, and the hydrolysate was tested on a paper chromatogram, no spot for alanine could be detected; so it seems that, if alanine is present in the polymer in the early stages of the reaction as a terminal residue, it is removed later by hydrolysis.

Table 2 shows the effect of varying the ratio of water to dione. Polymer formation ceases when this ratio is between 3 : 1 and 4 : 1. With the water–dione ratio 3 : 1, the concentration of dione after 24 hours (Table 2*a*) is 43·4/3 = 14·3 g. per 100 g. of water; after 41 hours (Table 2*b*) there is a small increase in polymer formation. With a water–dione ratio of 4 : 1 there is no polymer formation after 24 hours, and the concentration of dione is 46·0/4 = 11·5 g. per 100 g. of water. The lower limit of dione concentration for polymer formation to take place must therefore lie between 11·5 and 14·3 g. per 100 g. of water. The estimated solubility of the dione at 140° is 16·6 g. per 100 g. of water, so that ΔG for the reaction: dione (solid) ⟶ polymer (solid), lies between −0·11 and −0·31 kcal. mole^{-1} at 140°. The value estimated[1] for 180° was −0·26 kcal. mole^{-1}, so that ΔG appears to change little with temperature. It seems probable that for this reaction

TABLE 2. *Effect of varying the dione : water ratio.*

Water/ Dione	Percentage of total N as polymer	$-NH_2$	dione	peptide	NH_3 or $(NH_4)_2CO_3$	Mean D.P. of sol. peptides
			Time: 24 *hr.*			
0·5	33	6·0	51·5	14·4	0·6	2·4
1	65	18·8	17·9	17·9	1·6	0·95
2	31·5	21·6	45·5	20·7	0·4	0·96
3	5·0	41·8	43·4	47·7	1·2	1·15
4	0	26·2	46·0	53·0	0·9	1·79
			Time: 41 *hr.*			
1	60·5	23·3	10·9	27·6	1·8	1·18
2	40·0	24·5	26·2	32·2	1·0	1·32
3	11·0	42·0	29·8	55·5	2·2	1·32

both ΔH and ΔS are small, in accordance with the calculations by Dainton, Devlin, and Small[2] for polymerisation of six-membered rings.

The equivalent weight of the polymers was determined by titrating them in saturated calcium chloride solution with alkali after the addition of formaldehyde. A blank titration was necessary, in order to allow for acid in the formaldehyde and for ammonium salts in the calcium chloride. This method, which is a modification of that described by Sluyterman and Labruyere,[3] gave very reproducible results. The equivalent weight was also estimated by means of the absorption of Orange II (sulphanilic acid→β-napthol),[4] but this method showed certain anomalies; when these were eliminated, there was equivalence between the alkali titrations and the Orange II absorption, showing that the polymers contained equal numbers of carboxyl and amino-groups. A full account of this investigation will be published later.

[2] Dainton, Devlin, and Small, *Trans. Faraday Soc.*, 1955, **51**, 1710.
[3] Sluyterman and Labruyere, *Rec. Trav. chim.*, 1954, **73**, 347.
[4] Fraenkel-Conrat and Cooper, *J. Biol. Chem.*, 1944, **154**, 239.

In a polyamide melt the degree of polymerisation is determined by the homogeneous reaction:

$$x\text{-mer} + y\text{-mer} = (x + y)\text{-mer} + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

which may be expressed as:

$$-CO_2^- + -NH_3^+ = -CO{\cdot}NH- + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Then

$$K_1 = \{-CO{\cdot}NH-\}\{H_2O\}/\{-CO_2^-\}\{-NH_3^+\} \quad . \quad . \quad . \quad (3)$$

K_1 is dimensionless and is the same for all values of x and y, including the occasion when x or $y = 1$.[5] The symbols in braces refer to activities.

It will be assumed that eqns. (1)—(3) can be applied also to the solid polyglycine phase in the present case, but with the exception that K has a special value when x or $y = 1$. In glycine the carboxyl and amino-groups are sufficiently near each other to influence each other; this is not so for the higher peptides, or for the systems for which eqns. (1)—(3) have been tested experimentally.

In solid polyglycine the different polymer species are all present in a single phase, as they are in a melt, and from *X*-ray diffraction data on the lower peptides of glycine it is very probable that the carboxyl and amino-groups are closely associated, so that reaction is possible without disruption of the crystal lattice. Application of eqns. (1)—(3) to the solid polymer phase is therefore plausible, as a working hypothesis, and since it leads to a heat of reaction which is in agreement with the value deduced from heats of combustion it appears justified.

In order to apply eqn. (3), it is necessary to find expressions for the activities of water, $-CO{\cdot}NH-$, $-CO_2^-$, and $-NH_3^+$ in terms of experimentally measurable quantities.

Consider a weight of the polymer, having degree of polymerisation n, which contains 1 g.-atom of nitrogen. The molecular weight of the repeating unit in the polymer is 57, so that the required weight will be $(57 + 18/n)$ g. This quantity of polymer will contain $(1/n)$ equiv. of $-CO_2^-$ groups, $(1/n)$ equiv. of $-NH_3^+$ groups, and $(1 - 1/n)$ equiv. of $-CO{\cdot}NH-$ groups.

The following are taken as standard states for the reactants: for water, liquid water at the temperature of the reaction; for $-CO{\cdot}NH-$, the $-CO{\cdot}NH-$ group in the polymer of infinite chain length; for $-CO_2^-$ and $-NH_3^+$, these groups in the polymer of infinite chain length.

Let the number of equivs. of any of the groups per g.-atom of nitrogen be (x). In the polymer of infinite chain length the activity of the carboxyl and amino-groups will be (x), and we may put $a = (x)$, or $a \rightarrow (x)$ as $n \rightarrow$ infinity. Since charged groups are involved, the ratio $a/(x)$ will diverge from unity as the concentration of charged groups in the polymer increases, *i.e.*, as n decreases. But over a narrow range of values of n the ratio $a/(x)$ may be taken as constant (denoted by γ), in analogy with an activity coefficient in an aqueous solution of an electrolyte. Then, $\gamma \rightarrow 1$ as $n \rightarrow$ infinity.

In the calculations in the present paper, n varies from 9 to 13, and it will be assumed that over this range the variation in γ may be neglected. Further, it is assumed that γ does not vary appreciably with temperature, again in analogy with aqueous solutions.

The value of (x) for the $-CO{\cdot}NH-$ group varies only from 0·89 to 0·92; moreover, this group carries no charge. It should be possible to put $a = (x)$ without appreciable error.

Inserting the appropriate quantities in eqn. (3) gives:

$$K_1 = a_{H_2O}.n(n - 1)/\gamma^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The equation is dimensionless. As γ cannot be evaluated from the data at present available, it will be assumed that it is unity.

The degree of polymerisation of the polymers from 100° to 180°, and the corresponding values of K_1 calculated by means of eqn. (4) are given in Table 3. Since in the reaction some of the piperazine-2:5-dione is hydrolysed to glycine, the liquid phase is a solution of

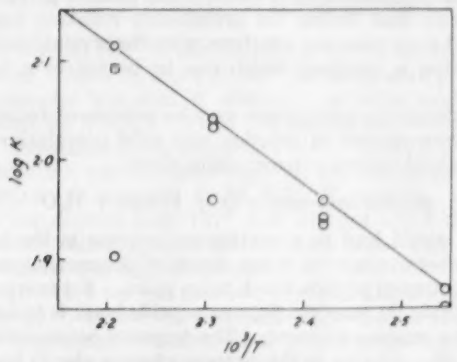
[5] Hermans, *J. Appl. Chem.*, 1955, **5**, 493.

glycine, in which the activity of water is less than unity. It is assumed that the activity of water in the polymer phase is the same as in the aqueous phase. From the yield of polymer the amount of glycine in the aqueous phase was calculated. The boiling points of

TABLE 3.

Temp.	Time (hr.)	Ratio, H_2O : Dione	Yield (%)	n	a_{H_2O}	K_1
180°	4	1	52	12·5	0·86	124
	7½	1	62	12·6	0·89	130
	3	2	13	10·1	0·87	80
160	8	1	60	10·7	0·88	91
	18	1	62	11·7	0·88	110
	48	1	60	11·6	0·88	108
140	41	1	60	10·7	0·88	91
	66	1	62	10·4	0·89	87
	120	1	58	10·7	0·88	91
	44	2	41	10·2	0·92	86
120	480	1	58	9·7	0·88	74
	650	1	60	9·5	0·88	71
100	720	1	68	7·7	0·91	47
	2500	1	68	7·9	0·91	49

a series of glycine solutions were determined in a Landsberg apparatus. If a particular solution boils at a temperature $T°$ and the vapour pressure of pure water at the same temperature is p atm., the activity of water in the glycine solution is $1/p$, approximately. It was assumed that in a solution of given concentration the activity of water relative to liquid water at the same temperature was constant from 100° to 180°. A graph was



constructed, which was linear, of a_{H_2O} against g. of glycine per 100 g. of water, and the activity of water in the aqueous phase was read off from it.

The values for K_1 obtained at 3 hours at 180°, at 8 hours at 160°, and at 30 and 104 days at 100° were not equilibrium values. The others may be. An attempt was made to approach the equilibrium from the other side. Polymer prepared at 180° was heated with water at 160° and 140°. After 18 hours at 160°, or 44 hours at 140°, there was no change in n. Heating for longer periods caused some decomposition, and both increases and decreases in n were observed. These results were without significance for determination of the equilibrium.

The values for K_1 given in Table 3 may be regarded as minimum values. The true equilibrium values may be greater; they can hardly be less.

In the Figure log K_1 is plotted against $1/T$. The line is drawn with a bias towards the higher values of K_1, in view of the possibility that they may be on the low side. The line is given by the expression:

$$\log K_1 = 3{\cdot}72 - 725/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

From this, for the reaction, x-mer + y-mer = $(x + y)$-mer + H_2O (liquid); $\Delta H = 3{\cdot}3$ kcal. mole^{-1} and $\Delta S = 17$ cal. mole^{-1} degree^{-1}.

Since glycine can be dehydrated to piperazine-2 : 5-dione at 140—180° in glycerol [6] or ethylene glycol,[7] and since it followed from the present work that the dione is thermodynamically unstable with respect to polyglycine at all temperatures from 60° to 180°, direct polymerisation of glycine to polyglycine appeared possible, and this was confirmed by experiment.

When glycine is heated with a small amount of hydrochloric acid in a sealed tube at a temperature above 140°, it is converted into polyglycine. The yield of polymer depends on the ratio of glycine to hydrochloric acid, and the results obtained by using 10N-hydrochloric are given in Table 4. No polyglycine is formed at 130°, and if tubes which have been heated to 140° are kept at 130° for 24 hours, the yield of polymer is reduced.

The essential conditions for the reaction appear to be a temperature above 140° and the presence of glycine as solid phase. Hydrochloric acid is not essential to the reaction; phosphoric acid, ammonium chloride, and sodium hydroxide are effective catalysts, or the reaction may be carried out with water only. However, hydrochloric acid gives the best yield and quality of polymer.

It is possible to carry out the reaction at atmospheric pressure in the following way. Sufficient water was added to the mixture of glycine and hydrochloric acid to dissolve all the solid at the boiling point. If this solution was evaporated immediately, glycine began to separate when the boiling point of the solution had risen to 115—117°. If the solution was first refluxed for 2 hours, and then evaporated, no solid separated. The boiling point of the solution rose steadily as the water was removed, and the residue became increasingly viscous. When the temperature had risen to 150—160° it was held there for a few hours, and the product was then extracted with water. The yield of polyglycine by this method varied greatly. It seems that during the preliminary refluxing some lower peptides of glycine are formed, and their presence interferes with the crystallisation of glycine, so that a supersaturated solution is obtained which can be heated to a temperature at which glycine can polymerise.

Polymerisation of glycine to polyglycine may be considered to take place by a heterogeneous reaction between glycine in solution and solid polyglycine, in which successive glycine molecules are added on to a polymer chain, thus :

$$\text{glycine} + x\text{-mer} = (x + 1)\text{-mer} + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This process by itself would lead to a continuous increase in the length of the polymer chains, and in the number average (n) of the degree of polymerisation. At the same time, however, hydrolysis of internal peptide bonds takes place. For every n molecules of glycine converted into polyglycine by reaction (6), one peptide bond is hydrolysed by the reverse of reaction (1), so that n remains constant. The degree of polymerisation is determined by K_1, according to eqn. (3). Glycine in the aqueous phase is also in equilibrium with soluble peptides and with piperazine-2 : 5-dione, but these are not here concerned. The equilibrium constant for eqn. (6) is given by :

$$K_2 = \{(x + 1)\text{-mer}\}\{H_2O\}/\{x\text{-mer}\}\{\text{glycine}\} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The standard state for glycine is solid glycine at the temperature of the reaction. The standard state for water is liquid water at the temperature of the reaction, as for eqn. (3). The standard state for the polymer is the solid polymer at the temperature of the reaction. In a polymer of number average degree of polymerisation n, the mole ratio [8,9] $(x + 1)$-mer to $(x$-mer) is $(n - 1)/n$, and the activity ratio will be the same. Eqn. (7) then becomes :

$$K_2 = (n - 1)\{H_2O\}/n\{\text{glycine}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Eqn. (8) defines the activity of water in a system containing solid glycine and solid polyglycine. If the system also contains a liquid phase, that is, if glycine is in equilibrium with its saturated solution, the system will contain four phases ; glycine solution, solid

[6] Balbiano, *Ber.*, 1901, **34**, 1501; Maillard, *Ann. Chim.*, 1914, **1**, 519; **2**, 210.
[7] Sannie, *Bull. Soc. chim.* (*France*), 1942, **9**, 487.
[8] Flory, *Chem. Rev.*, 1946, **39**, 174.
[9] Meggy, *J.*, 1953, 796.

glycine, solid polyglycine, and water vapour. The system contains only two components, since all glycine peptides and polymers can be regarded as (x Glycine $-$ H_2O). Therefore in the presence of a liquid phase the system is invariant. There can be only one temperature at which four phases can co-exist, and this is a transition temperature. At all other temperatures, if a liquid phase is present, the solid phase may be either glycine or polyglycine. If both are present, no liquid phase can exist at equilibrium.

These conclusions are in agreement with the experimental results. The transition temperature lies between 130° and 140°. Below this temperature glycine is the stable solid phase in the presence of glycine solution; above it, polyglycine is the stable solid phase. Since polyglycine is stable at the higher temperature, the reaction n Glycine → Polyglycine (n-mer) + $(n-1)H_2O$ must be endothermic.

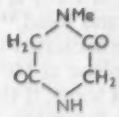
Experimental determination of K_2 is difficult. It is not possible to measure the activity of water for the system (solid glycine—solid polyglycine) over a range of temperatures, since equilibrium is not established in the absence of an aqueous phase. Polymer is not present in the presence of an aqueous phase below the transition temperature, at any rate in measurable amounts, since its solubility is very low. Consequently it is not possible to determine n. Above the transition temperature polymer is present in quantity, and n can be determined. The activity of water can also be determined from its partial pressure. But it is difficult to devise a simple method for determining the activity of glycine in the aqueous phase; even the determination of its concentration is rendered difficult by the presence of appreciable amounts of soluble peptides.

A single determination of K_2 at the transition temperature is possible, since at this temperature the activity of glycine is unity. It is only necessary to determine n, and the partial pressure of water.

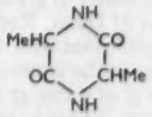
Glycine was polymerised at 140°, in the presence of hydrochloric acid in a tube attached to a mercury manometer. After 24 hours at 140° the tubes were placed in a Silicone bath at 137°, and the manometer was read at intervals; a value was reached after 1 hour which remained constant for 6 hours. From the manometer reading the partial pressure of water was 1·2 atm. Since the vapour pressure of water [10] at 137° is 3·27 atm., $a_{H_2O} = 0{\cdot}36$. The degree of polymerisation was 12; from eqns. (4) and (5) the expected value is 16. If the transition temperature is assumed to be 137°, $K_2 = 0{\cdot}33$. If the transition temperature differs by a few degrees from 137°, this will not affect the value of K_2 at the transition temperature appreciably, since the variation of $(n-1)/n$ with temperature will be negligible, and the variation of a_{H_2O} will be small.

The transition temperature for the reaction, glycine(solid)→polyglycine(solid) + H_2O (liquid), being taken as 137°, $\Delta G = 0{\cdot}89$ kcal. mole^{-1} (glycine) at 137°.

Reactions of Other Piperazine-2 : 5-diones and Amino-acids.—Attempts to polymerise substituted piperazine-2 : 5-diones and amino-acids other than glycine were not successful. Heating sarcosylglycine with an equal weight of water at 140° for 20 hours converted it quantitatively into 1-methylpiperazine-2 : 5-dione (II), and no polymer was formed.



(II)



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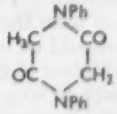
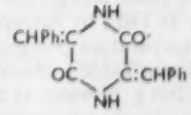


(IV)



(V)

Under the same conditions glycylglycine gave polymer. 3 : 6-Dimethylpiperazine-2 : 5-dione (DL-alanine anhydride) (III) was hydrolysed to alanine and alanylalanine without polymer formation. 1 : 4-Diphenylpiperazine-2 : 5-dione (IV) (from *N*-phenylglycine [11]) and 3 : 6-dibenzylidenepiperazine-2 : 5-dione (V) (from benzaldehyde and piperazine-2 : 5-dione [12]) remained unchanged.

[10] International Critical Tables, Vol. III, p. 233.
[11] Bischoff and Hausdorfer, *Ber.*, 1892, **25**, 2271.
[12] Sasaki, *Ber.*, 1921, **54**, 163.

Tazawa [13] states that silk is depolymerised when heated in anhydrous ethylene glycol or glycerol to a mixture of diketopiperazines. This appears to be the reverse of the polymerisation of piperazine-2 : 5-dione; however, attempts to convert polyglycine into piperazine-2 : 5-dione by heating it in anhydrous glycerol have not been successful.

Attempts to polymerise amino-acids other than glycine were not successful. α-Amino-*iso*butyric acid was unchanged when heated with a little hydrochloric acid at 140° for 24 hours. At 220—240° a trace of a sublimate was formed, which may have been the anhydride, 3 : 3 : 6 : 6-tetramethylpiperazine-2 : 5-dione. On prolonged heating at this temperature, considerable pressure was developed, and the tubes burst. From the odour it seemed that decomposition had taken place to *iso*propylamine and carbon dioxide.

DL-Phenylalanine was partly decomposed under the reaction conditions, with the formation of tar. L- and DL-Alanine gave dark viscous products, completely soluble in water.

The higher amino-acids are less soluble than glycine; consequently the activity of water in their saturated solutions at 140° is greater than it is in the saturated solution of glycine at this temperature, and this would tend to prevent polymerisation. Two experiments were carried out in which glycine, DL-alanine, and 10N-hydrochloric acid were heated at 140°. The proportions of glycine to acid were 2 : 1 and 2·5 : 1, which, from Table 4, is

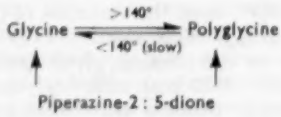
TABLE 4. *Direct polymerisation of glycine at* 140°.

Time of heating, 18 hr.; 1 ml. of 10N-HCl.

Glycine (g.)	2·0	2·2	2·6	2·8	3·5	5·0
Polymer (%)	0	0	?	5	20	53
Mean D.P. of sol. fraction	—	1·33	1·52	1·58	1·60	1·65

about the marginal ratio for polymer formation. Consequently, the activity of water in these experiments should be about the same as in the polymerisation of glycine. The product was almost completely soluble in water in both cases. However, the biuret reaction was pink, and the ratio of total nitrogen to amine-nitrogen was about 2·5. It seems that some peptide formation takes place under these conditions.

Discussion.—The relation between solid glycine, solid piperazine-2 : 5-dione, and polyglycine, in the presence of water, is :



In the presence of an aqueous phase, the dione is unstable with respect to glycine and polyglycine at all temperatures.

In the polymerisation of piperazine-2 : 5-dione, equilibrium was not reached between the polymer phase and glycine in solution. The solubility of glycine in water is 112 g./100 g. of water at 140°, by extrapolation from the data of Dunn, Ross, and Read,[14] and at or near this temperature polyglycine should be in equilibrium with the saturated solution of glycine. From Table 1, the concentration of glycine in the aqueous phase at 140° increases from 50 g./100 g. of water at 24 hours, to 80 g./100 g. of water at 114 hours, if the whole of the soluble nitrogen is regarded as glycine-nitrogen. This is still below the saturation value, and it seems that hydrolysis of the polymer is extremely slow, presumably because it is controlled by the rate of diffusion of the glycine formed by hydrolysis.

Although equilibrium was not established between the polymer phase and glycine in solution, it is believed that equilibrium was established between the various polymer species in the polymer, and water in the aqueous phase. Replicate experiments at the same temperature gave the same value of K_1, which did not change with time. The plot of log K_1 against $1/T$ was linear, and the heat of reaction calculated from the slope was

[13] Tazawa, *Acta Phytochim.* (*Japan*), 1942, **13**, 57.
[14] Dunn, Ross, and Read, *J. Biol. Chem.*, 1933, **103**, 579.

consistent with the heat of formation for the peptide bond in glycine-peptides calculated from combustion data.

The heats of combustion of glycine-peptides have been determined by Wrede.[15] The heat of formation of glycylglycine has been calculated by Borsook and Dubroff[16] from Huffman's data.[17] The calculated values for the heat of formation of the peptide bond in a number of glycine peptides (Table 5) show that the heat of formation of the peptide

TABLE 5. *Heat of formation of the peptide bond.*

Reaction	H (kcal.)	H per –CO·NH– (kcal.)	Ref.
$G + G = G_2 + H_2O$	5·50	5·50	16
$3G = G_3 + 2H_2O$	9·68	4·84	15
$4G = G_4 + 3H_2O$	13·10	4·36	,,
$G + G_2 = G_3 + H_2O$	4·18	4·18	,,
$G + G_3 = G_4 + H_2O$	3·42	3·42	,,
$2G$ = piperazinedione + $2H_2O$	7·90	3·95	,,

bond for successive glycyl residues tends to a value between 3 and 4 kcal. From the heat evolved in the enzymic hydrolysis of lactoglobulin, Linderstrøm-Lang[18] arrived at a similar estimate for the peptide bond in proteins. The value of 3·3 kcal. calculated from eqn. (5) is in good agreement with the thermochemical results. From the heat of formation of piperazine-2 : 5-dione, the heat of the reaction, piperazine-2 : 5-dione→polyglycine, is −0·65 kcal. per –CO·NH–. This is probably within the limits of error of the combustion data, but it indicates that ΔH for this reaction is small, in agreement with theory[2] and with the polymerisation experiments.

Since only a single determination of K_2 could be made it was not possible to determine ΔH for reaction (6) from the experimental results. However, it is probably not greatly different from the value 3·3 kcal. mole^{-1} for the reaction between two peptides, since from Table 5, for $G + G_3 = G_4 + H_2O$, $\Delta H = 3{\cdot}42$ kcals. If it be assumed that ΔH for reaction (6) is 3·3 kcal., then since $\Delta G = 0{\cdot}89$ at 137°, $\Delta S = 5{\cdot}9$ cal. mole^{-1} degree^{-1}.

Thus, assuming that $\Delta H = 3{\cdot}3$ kcal. mole^{-1} for reactions (1) and (6), $\Delta S = 17$ cal. mole^{-1} degree^{-1} for reaction (1) and 5·9 cal. mole^{-1} degree^{-1} for reaction (6). The difference of 11·1 cal. in the entropy for the two reactions is due mainly to the difference in the entropy of ionisation of glycine and the higher peptides.[19] For glycine, for the reaction,[20]

$$NH_3^+{\cdot}CH_2{\cdot}CO_2^- = NH_2{\cdot}CH_2{\cdot}CO_2H$$

$\Delta S = -1{\cdot}6$ cal. mole^{-1} degree^{-1}. For the higher glycine peptides[21] at 25°, $pK_a = 3{\cdot}00$, $pK_b = 7{\cdot}60$. For the conversion of the ionised into the non-ionised form, $\Delta G = 6{\cdot}24$ kcal. mole^{-1}. The heat of ionisation of glycine[20] is 9·65 and for glycyl-glycine 10·21 kcal. mole^{-1} at 25°. It has not been determined for the higher peptides, but if it is assumed to be the same as for glycylglycine, then for the higher peptides $T\Delta S = 3{\cdot}97$ kcals. at 25°, and $\Delta S = 13{\cdot}3$ cal. mole^{-1} degree^{-1}. The difference in the ionisation entropy of glycine and the higher peptides is therefore about 14·9 units at 25°, compared with a difference of 11·1 for the entropies of reactions (1) and (6) at 140°.

The difference in the ionisation entropy of glycine and the higher peptides is due to the increasing separation of the charged centres in the peptides.[19] For the tripeptide the separation is already so great that the carboxyl and amino-groups no longer influence each other. The same is observed when the groups are separated by a hydrocarbon chain. For 6-aminohexanoic acid,[21] $pK_a = 4{\cdot}43$, $pK_b = 10{\cdot}75$; these are practically the same as

[15] Wrede, *Z. phys. Chem.*, 1910, **75**, 92.
[16] Borsook and Dubroff, *J. Biol. Chem.*, 1940, **132**, 308.
[17] Huffman, *J. Phys. Chem.*, 1942, **46**, 885.
[18] Linderstrøm-Lang, Proc. 9th Solvay Congr., Brussels, 1953.
[19] *Idem*, Proc. 6th Int. Congress Exp. Cytology, Stockholm, 1950, p. 1; Meggy, *J. Appl. Chem.*, 1954, **4**, 154.
[20] Smith, *J. Biol. Chem.*, 1942, **146**, 193.
[21] Glasstone and Hammel, *J. Amer. Chem. Soc.*, 1941, **63**, 243; Cohn and Edsall, "Proteins, Amino-acids, and Peptides," Reinhold Publ. Corp., New York, 1943.

for an aliphatic acid and an aliphatic amine respectively. Consequently the values for the equilibrium constants K_1 and K_2 should be the same; this has been confirmed [5] for the polymerisation at 220°.

The dissociation constants of other α-amino-acids are approximately the same as for glycine,[21] and the dissociation constants for the α-amino- and the carboxyl groups in higher peptides are about the same as for the glycine-peptides.[21] It is probable that the heat and entropy for the formation of a peptide bond from an uncharged amino- and an uncharged carboxyl group are about the same for all α-amino-acids and peptides. It follows that the heat and entropy for the formation of a peptide bond between any two amino-acids will not differ greatly, on the average, from the values for glycine. This is supported by the estimate for the heat of hydrolysis of the peptide bonds in β-lactoglobulin.

At 37° the value of K_1 is 23·8, from eqn. (5), and $n = 5{\cdot}4$. It follows that if polyglycine of high molecular weight is treated with an endopeptidase capable of hydrolysing internal, but not terminal, peptide bonds, the polymer will be degraded to a number average degree of polymerisation of 5·4, corresponding to the hydrolysis of 15·7% of all the peptide bonds. The value of K_2 at 37° is 0·09; if the partially hydrolysed polymer is treated with a carboxy- or amino-peptidase, it will be hydrolysed completely to glycine. On the other hand, the original polymer of high molecular weight will be only slowly attacked by a carboxy- or amino-peptidase, as the number of terminal groups present will be small.

These conclusions resemble qualitatively and quantitatively the action of digestive enzymes on proteins. Pepsin hydrolyses only 15—20% of the peptide bonds; complete hydrolysis of the remainder takes place in the presence of trypsin and erepsin. The action of these enzymes on intact protein is slow, but it is rapid on protein which has been treated with pepsin. However, the action of enzymes on proteins is greatly influenced by specific action on particular types of peptide bond.

Since polyglycine is thermodynamically unstable with respect to glycine at 37°, direct formation of polymers from glycine at this temperature is not possible. Yet in biological systems the synthesis of proteins takes place from very low concentrations of amino-acids. If the heat and entropy of formation of the peptide bond in proteins are not greatly different from those for polyglycine, this synthesis must require a supply of energy. The most probable source is the so-called "high-energy" phosphate bond, usually a P–O–P bond, such as exists in adenosine triphosphate. It is known that this can bring about the synthesis of glutamine from glutamic acid and ammonia,[22] and of hippuric acid from glycine and benzoic acid,[23] and that the reactions are reversible. For the reaction,[24]

$$\text{ATP} + \text{H}_2\text{O} \rightleftharpoons \text{ADP} + \text{phosphate} \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$\Delta G = -8{\cdot}00 \pm 0{\cdot}80$ kcal. at 25° and pH 7·0. For reaction (6), $\Delta G = 1{\cdot}83$ kcal. at 37°. Assuming −8·00 kcal. for reaction (9) at 37°, and combining reactions (6) and (9), we have:

$$\text{Glycine} + (x\text{-mer}) + \text{ATP} = (x+1)\text{-mer} + \text{ADP} + \text{phosphate} \quad . \quad . \quad (10)$$

for which $\Delta G = -6{\cdot}17$ kcal. at 37° and $K_3 = 2{\cdot}3 \times 10^4$, where:

$$K_3 = \{(x+1)\text{-mer}\}\{\text{ADP}\}\{\text{Phosphate}\}/\{x\text{-mer}\}\{\text{ATP}\}\{\text{Glycine}\} \quad . \quad . \quad (11)$$

The concentration of amino-acids in blood plasma is approx. 4×10^{-3} mole/l.; the concentration of phosphate [25] is approx. 10^{-3} mole/l. For eqn. (6) the standard state for glycine is the solid; at 37° the saturated solution is about 4M, so that the activity of glycine (solid) in a 4×10^{-3}M-solution is about 10^{-3}. For phosphate in eqn. (9) the standard state is the 1M-solution at pH 7·0. By inserting these values in eqn. (11), and putting $\{(x+1)\text{-mer}\}/\{x\text{-mer}\} = 1$, since the degree of polymerisation will be large, we have $\text{ADP}/\text{ATP} = 2{\cdot}3 \times 10^4$.

This signifies that in a solution 4×10^{-3}M with respect to glycine and 10^{-3}M with respect

[22] Levintow and Meister, *J. Biol. Chem.*, 1954, **209**, 265.
[23] Lipmann, *Fed. Proc.*, 1949, **8**, 597.
[24] Gutfreund, *Ann. Reports*, 1954, **51**, 301.
[25] Cameron, "Textbook of Biochemistry," Churchill, London, 1933.

to phosphate, and containing adenosine di- and tri-phosphate, the formation of polyglycine is possible thermodynamically if the molar ratio ADP/ATP is less than $2{\cdot}3 \times 10^4$. It should be noted that the ratio of the adenosine phosphates, not their total concentration, is the determining factor. The total concentration may be quite small. Provided that glycine is supplied at the right level, and the ADP/ATP ratio is maintained at the right level by some other reaction, *e.g.*, one involving the oxidation of carbohydrate, the synthesis of polyglycine could continue indefinitely.

The degree of polymerisation of the polymer will be determined by the reaction:

$$-CO_2^- + -NH_3^+ + \text{ATP} = -CO{\cdot}NH- + \text{ADP} + \text{Phosphate} \quad . \quad . \quad (12)$$

which is the combination of eqns. (2) and (9). Here we have:

$$K_4 = n(n-1)\{\text{phosphate}\}\{\text{ADP}\}/\{\text{ATP}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Since the solutions are 10^{-2}—10^{-3}M, a_{H_2O} may be taken as 1. For reaction (2) at 37°, $\Delta G = -2{\cdot}00$ kcal.; for reaction (9), $\Delta G = -8{\cdot}00$ kcal.; so that for reaction (12), $\Delta G = -10{\cdot}00$ kcal., and $K_4 = 10^7$. Putting $\{\text{phosphate}\} = 10^{-3}$, and $(\text{ADP})/\text{ATP} = 2{\cdot}3 \times 10^4$, gives $n = 660$.

If the ratio $\{\text{ADP}\}/\{\text{ATP}\}$ is less than $2{\cdot}3 \times 10^4$, synthesis is possible from concentrations of glycine less than 4×10^{-3}, and the degree of polymerisation of the polymers will be greater than 660. It seems that, if the heat and entropy of formation of the peptide bond between any two naturally occurring amino-acids are on the average not greatly different from the values for glycine, the energy necessary for protein synthesis from amino-acids at the concentrations at which they are present in biological systems, to degrees of polymerisation such as are found in proteins, can be supplied by adenosine triphosphate or by any other compound at the same energy level, such as phosphocreatine. The energy available from the hydrolysis of a P–O–(C) bond, such as is found in adenosine monophosphate, glucose phosphates, or nucleic acids, is probably insufficient for protein synthesis. The energy available from the hydrolysis of an inorganic P–O–P bond, as in pyrophosphate or polyphosphate, is sufficient in principle to polymerise glycine in aqueous solutions at low temperatures. But it is necessary to provide a mechanism for coupling the hydrolysis of the P–O–P bond with the synthesis of the peptide bond. If solutions of glycine and sodium pyrophosphate or sodium polyphosphate (Calgon) are heated, there is a slow hydrolysis of the P–O–P bond, but no synthesis of polyglycine.

Experimental.

Determination of the Degree of Polymerisation.—A weighed amount of the polymer, dried at 100° for 1 hr., was dissolved in 42% calcium chloride solution, with warming if necessary. Dissolution of the polymer required ½—1 hr. Formaldehyde solution (40%; 10 ml.) was added, and the solution titrated with 0·1N-potassium hydroxide (to phenolphthalein). A control titration was carried out. The degree of polymerisation of the polymer was given by (equiv. wt.—18)/57.

Polymerisation of Glycine.—(a) *With hydrochloric acid.* Glycine (10 g.) was heated with concentrated hydrochloric acid at 140° (sealed tube) for 24 hr. and the product then extracted with boiling water. The solid material was separated at the centrifuge, washed twice with water, then twice with methanol, and dried at 100° or in a vacuum-desiccator ($CaCl_2$). The yield (4 g., 53%) was the same with 2N-acid and was not increased by heating for 65 hr.

(b) *With sodium hydroxide.* Glycine (5 g.) and 2N-sodium hydroxide (1 ml.) at 150° gave, in 19 hr., 1·3 g. (33%) of polymer.

Glycine (5 g.) with ammonium chloride (1·5 g.) in water (1 ml.) at 150° for 19 hr., with 85% phosphoric acid (2 ml.) at 140—150° for 60 hr., or with water at 140—150° for 68 hr. gave 20, 26, or 8%, respectively of polymer.

Polymerisation under Atmospheric Pressure.—Glycine (75 g.), concentrated hydrochloric acid (25 ml.) and water (60 ml.) were heated under reflux for 2 hr., then the water was distilled off during 1—2 hr., until the temperature was 140°. The mixture was kept at 140—150° for 18 hr. The product was boiled with water (150 ml.) until it disintegrated, then dissolved in a solution of calcium chloride (anhyd.; 800 g.) in water (1·2 l.), stirred with charcoal (10 g.) for 30 min. and filtered. The pale yellow solution was diluted to 5 l. and the polymer collected

at the centrifuge, washed with water and methanol, and dried at 100°. It formed a white powder (24 g., 42%).

Co-polymerisation of Glycine and DL-*Alanine.*—Glycine (2·5 g.), DL-alanine (2·5 g.), and concentrated hydrochloric acid (1 ml.) were heated for 19 hr. at 140°. The product was liquid when hot, except for a small residue, but solidified on cooling. It was dissolved in hot water (50 ml.) in which 0·1 g. was insoluble. The solution was decolorised with charcoal and filtered. The biuret reaction was magenta-red. Total N was determined by Kjeldahl's method, terminal N by neutralisation to methyl-red, addition of formaldehyde, and titration with alkali (to phenolphthalein). The ratio, total N : terminal N, was 2·6. In a second experiment, with 2 g. of glycine and 3 g. of alanine, the ratio was 2·5. No crystalline material was obtained from the solutions.

α-Amino*iso*butyric acid (5 g.) and 2N-hydrochloric acid (2 ml.) were unchanged during 19 hr. at 140—150°. Heating for 18 hr. at 220—240° gave only a trace of sublimate.

DL-Phenylalanine (1 g.) and 2N-hydrochloric acid (1 ml.) in 16 hr. at 140—150° gave only a little tar and an odour of phenylacetaldehyde.

p-Aminobenzoic acid (3 g.) was decomposed by water (3 g.) in 66 hr. at 140—160° completely to aniline and carbon dioxide.

Sarcosylglycine (1 g.) and water (1 g.) in 20 hr. at 140° gave a clear yellow solution; addition of alcohol (8 ml.) gave a trace of crystalline material (glycine ?). Evaporation of the filtrate and crystallisation of the residue (0·9 g.) from ethyl acetate gave material of m. p. 139—142° alone or mixed with sarcosylglycine anhydride.

1 : 4-Diphenylpiperazine-2 : 5-dione (3 g.) was unchanged by water (3 g.) in 65 hr. at 140—160°.

3 : 6-Dibenzylidenepiperazine-2 : 5-dione (3 g.) was unchanged by water (3 g.) for 65 hr. at 140—160°. After 24 hr. at 220—240° it was decomposed (odour of phenethyl alcohol): crystallisation of the product from water (charcoal) gave a small amount of crystals, m. p. 69—72°, probably impure phenylacetic acid.

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294. *Liquid Metals. Part IV.* The Wetting of Zinc by Liquid Sodium: the Significance of the Critical Wetting Temperature.*

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The wetting of metallic zinc by liquid sodium has been studied by measurement of contact angles over ranges of time and temperature. Electropolished zinc surfaces show a critical wetting temperature near 160°, and chemical reaction between sodium and the zinc phosphate film deposited during electropolishing is shown to be responsible for this. No critical wetting temperature is observed for abraded zinc plates. Rates and mechanisms of wetting are discussed from the point of view of diffusion through surface films of zinc phosphate and zinc oxide and the formation of the intermetallic compound $Zn_{13}Na$. The condition of the surface of zinc after wetting by sodium has been studied microscopically.

FACTORS which influence the wetting of a solid metal by a liquid metal fall into two distinct categories. First, there are those resulting from properties of the pure metals, such as surface tension, atomic volume, and electronic structure; an early attempt was made by Hildebrand and his co-workers [1] to relate wettability with a fundamental property. The limited data available suggest that the two metals must form a layer of intermediate composition at the interface before wetting can occur; this approach permits wetting to be related to some measurable property of the metal system. Secondly, there are those factors which arise from the presence of films at the solid metal surface.

Several workers have suggested that wetting only occurs rapidly above a critical

* Part III, *J.*, 1955, 3047.

[1] Hildebrand, Hogness, and Taylor, *J. Amer. Chem. Soc.*, 1923, **45**, 2828.

wetting temperature. This has been observed for the systems bismuth–copper, tin–molybdenum, tin–copper,[2] and lead–nickel,[3] when a gas is used as the third phase, and in certain other systems when the third phase is a flux.[4,5] Miller, Ewing, Hartman, and Atkinson [6] studied visually the wetting of nickel and of steel by liquid sodium, and quoted wetting temperatures. Winkler and Vandenburg [7] employed molybdenum, nickel, and steel specimens as ribbons of known electrical resistance. A wetting film of sodium acts as a low-resistance conductor in parallel, and its presence is revealed by change in electrical resistance. In these experiments the specimens were coated with oils and the values have no significance as fundamental properties of the liquid metal–solid metal systems. In spite of these observations of the phenomenon, little attempt has been made to seek a reason for critical wetting.

The work to be described in this and later papers concerns factors governing the wetting of metals by liquid sodium, starting with the transition metals, and first with the zinc group. The readiness with which the metals form intermetallic compounds decreases in the order Hg > Cd > Zn, as shown by the number of compounds revealed in the phase diagrams: Hg_4Na, Hg_2Na, Hg_8Na_7, $HgNa$, Hg_2Na_3, Hg_2Na_5, $HgNa_3$;[8] Cd_6Na, Cd_2Na;[9] $Zn_{13}Na$.[10,11,12] At 200°, the solubility of mercury in sodium is 44 atoms %, and when clean mercury is placed in liquid sodium it will clearly be wetted immediately. The solubility of cadmium in sodium is 5 atoms % at 200°. A thin plate of cadmium placed in liquid sodium (at 100° and above) was wetted immediately: within a few minutes the plate grew thick because of the formation of the intermetallic compound, some of which also dissolved in the sodium. The case of zinc is of particular interest, since although one intermetallic compound is formed,[10] the solubility of zinc in sodium is not detectable below the melting point of the compound $Zn_{13}Na$ (557°).

Results and Discussion

Electropolished Plates.—Contact angles were measured by the vertical-plate technique. A thin plate of zinc (partly immersed in liquid sodium) was suspended from an arm attached to a torsion wire; the forces acting on the plate include the surface tension of sodium (γ) acting at some angle θ, and from the balance of forces the term $\gamma \cos \theta$ is evaluated. The apparatus and procedure are described in Part I,[13] and the value of γ used in deriving contact angles is that already determined by this technique.[13] In each measurement the plate was drawn up through the surface in stages, and the contact angle recorded at each stage. The value of θ decreased to a steady minimum value, which represents the true receding angle. The periods of time recorded in this paper as "times of immersion" are the times elapsing since the plate was first immersed in sodium. During each run the plate was normally kept immersed, and was only withdrawn during the actual measurement of contact angle.

When an electropolished (but not degreased) zinc plate is used at a temperature of 180°, θ falls slowly during 30 min. to 20°, and thereafter remains at about this value. When the plate was degreased for 4 hr. in a Soxhlet extractor with acetone and withdrawn from hot acetone, wetting was almost complete after 30 sec., and θ reached 0° within 10 min. However, when a plate was given identical treatment but was withdrawn from acetone after the latter had been allowed to cool, θ was 40° after 10 min., and 0° after 20 min.

[2] Tammann and Ruhenbach, *Z. anorg. Chem.*, 1935, **223**, 192.
[3] Bailey and Watkins, *J. Inst. Metals*, 1951/2, **80**, 57.
[4] Daniels and Macnaughton, Tech. Pub. Internat. Tin Research Development Council, Series B, 1937, p. 6.
[5] Lakin, *Trans. Faraday Soc.*, 1938, **34**, 1384.
[6] Naval Research Laboratory (U.S.A.), Report C—3105, April 1947.
[7] Knolls Atomic Power Laboratory Report KAPL—P—231, December 1949.
[8] See Hansen, "Aufbau der Zweistofflegierungen," Julius Springer, Berlin, 1936, pp. 790—797.
[9] *Ibid.*, pp. 435—437.
[10] Mathewson, *Z. anorg. Chem.*, 1906, **48**, 196.
[11] Ketelaar, *J. Chem. Phys.*, 1937, **5**, 668; Zintl and Haucke, *Z. Electrochem.*, 1938, **4**, 104.
[12] Shoemaker, Marsh, Ewing, and Pauling, *Acta Cryst.*, 1952, **5**, 637.
[13] Addison, Kerridge, and Lewis, *J.*, 1954, 2861.

Traces of organic contamination thus have a pronounced effect on rates of wetting by sodium (see also Bondi [14]).

Above 160°, the rate of wetting of thoroughly degreased plates increases with temperature (Fig. 1). Below 160°, a different behaviour is observed (Fig. 2). There is a delay (which increases rapidly as temperature decreases) during which the angle passes through a maximum, and the contact angle then falls to 0° at a rate which falls with decreasing temperature. From a graph of the times required for complete wetting against temperature, it is clear that there is a critical wetting temperature near 160°, and on either side of this temperature two quite different processes of wetting are operating.

Nature and Thickness of Film on Electropolished Zinc.—Electropolishing produces a

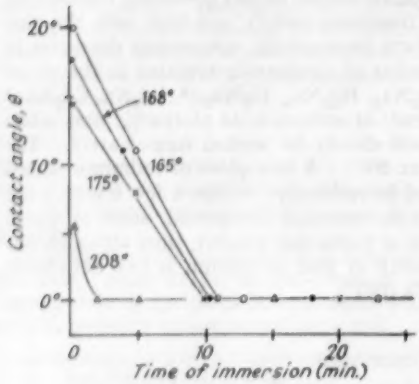


FIG. 1. *Wetting of electropolished zinc by sodium above 160°.*

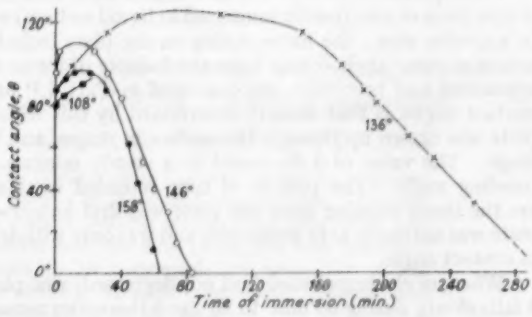


FIG. 2. *Wetting of electropolished zinc by sodium below 160°.*

solid film on a metal surface.[15] Raether [16] concluded that the film produced by electropolishing zinc in orthophosphoric acid was more than 50 Å thick; Jacquet and Jean [17] found the phosphorus present on electropolished zinc, after the plate had been washed in alcoholic phosphoric acid and then water, to be 0·6—2·3 × 10^{-7}g./cm.^{2}. The film being assumed to consist of anhydrous zinc phosphate (d 4·0 in the massive state [27]), our calculations indicate a film thickness of 20—70 Å. The film may be appreciably thicker before washing; in analogous experiments on electropolished copper, Jacquet and Jean [17] found the washed copper film to contain about the same quantity of phosphorus as does the zinc film, whereas the film on unwashed electropolished copper is about 1000 Å thick.[18]

[14] Bondi, *Chem. Rev.*, 1953, **52**, 418.
[15] Hoar and Farthing, *Nature*, 1952, **169**, 324.
[16] Raether, *Métaux et Corrosion*, 1949, **24**, 148.
[17] Jacquet and Jean, *Rev. Métallurgie*, 1951, **48**, 537.
[18] Raether, *Métaux et Corrosion*, 1947, **22**, 2.

In the present experiments a tracer technique was used to study the film: 1 ml. of a dilute aqueous solution of phosphoric acid containing 1 mc activity of ^{32}P was added to an orthophosphoric acid bath in which a plate was electropolished under normal conditions. From the ratio of active to inactive phosphorus, it was found that $(7{\cdot}0 \pm 2) \times 10^{-6}$ g. of phosphorus per cm.^{2} were deposited. The plate was then wetted with sodium at 175°, washed quickly with water to remove the sodium film, rinsed in pure acetone, and dried in hot air; all the activity was retained on the plate. The latter was then dissolved in dilute hydrochloric acid, and sodium phosphate added to the solution. The total phosphate was precipitated as magnesium ammonium phosphate, and all the activity was found in the precipitate. Since these conditions are not such as to convert phosphide, phosphite, etc., into phosphate, there is little doubt that the phosphorus was deposited on the metal surface during electropolishing as an orthophosphate, and the radioactivity measurements indicate a film thickness of 1000 ± 300 Å.

Reaction of Sodium with Anhydrous Zinc Phosphate.—Pure anhydrous zinc phosphate, shaped into thin blocks, was immersed in liquid sodium at various temperatures. The observations are collected in the annexed Table. The critical reaction temperature coincides

Fused $Zn_3(PO_4)_2$		Sintered $Zn_3(PO_4)_2$	
Temp.	Observation	Temp.	Observation
<160°	No wetting by sodium; $Zn_3(PO_4)_2$ block gradually became black	<162°	No wetting by sodium
			No reaction, but block gradually blackened
160°	Vigorous reaction: block disintegrated	162°	Some visible reaction, but slower than with fused $Zn_3(PO_4)_2$
>160°	Vigorous reaction	>162°	Reaction becomes more vigorous with increasing temperature

with the critical wetting temperature for zinc metal in sodium. Analysis of reaction products showed the reaction to be

$$6Na + Zn_3(PO_4)_2 \xrightarrow{160°} 3Zn + 2Na_3PO_4$$

The darkening in colour of the zinc phosphate block below 160° probably results from penetration of sodium into the block. The anhydrous sodium phosphate produced above 160° is not rapidly soluble in water, since it was not removed on washing the plate in water after the tracer experiment.

Mechanism of Wetting.—Below 160° the zinc phosphate film does not react; since wetting eventually takes place in spite of this, we must assume that diffusion of zinc atoms or ions through the film takes place, and that complete wetting only occurs when sufficient zinc has migrated through the film to give a continuous layer of the compound $Zn_{13}Na$. Tammann [20] observed that diffusional mobility in salts became appreciable when the absolute temperature reached half of the m. p. of the salt. Since the m. p. of zinc phosphate is about 900°, the temperatures used in these experiments appear to be low for normal diffusion, but this may be offset by the short distances involved. An Arrhenius plot of log $(1/T_w)$ (where T_w is time for complete wetting) against the reciprocal of absolute temperature over the range below 160° indicates an "activation energy" (E) of the order of 35 kcal. A similar value of E is obtained from the slopes of the linear parts of the wetting curves (Fig. 2). This might be the activation energy for diffusion of Zn^{2+} through a $Zn_3(PO_4)_2$ film, and it is of interest to compare it with $E = 37{\cdot}8$ kcal. for diffusion of Cu^+ through Cu_2O [21] at 800—1000°, and $E = 73{\cdot}7$ kcal. for diffusion of Zn^{2+} through ZnO at 800—1370°.[22]

The contact angle–time curves in Fig. 2 are also consistent with a diffusion mechanism.

[19] Cabrera and Mott, *Rep. Prog. Phys.*, 1948–9, **12**, 163.
[20] Tammann, *Z. anorg. Chem.*, 1926, **157**, 321.
[21] Castellan and Moore, *J. Chem. Phys.*, 1949, **17**, 41.
[22] Lindner, Campbell, and Akerström, *Acta Chem. Scand.*, 1952, **6**, 457; Secco and Moore, *J. Chem. Phys.*, 1955, **23**, 1170.

The compound $Zn_{13}Na$ is the only one formed; we may suppose that intermetallic compound formation does not occur until sufficient zinc atoms have diffused to the surface. Since each sodium atom in the compound $Zn_{13}Na$ is surrounded by 24 zinc atoms at the vertices of a "snub cube," [12] this may require several atomic layers of zinc. Until this stage is reached, no wetting can occur. The time at which wetting commences will depend on diffusion rates, and should therefore be highly dependent on temperature. When wetting commences, the contact angle changes linearly with time. The zinc metal surface is composed of crystal faces of different orientation, which react to differing degrees. The thickness of the electropolishing film, and the ease with which zinc atoms diffuse from the crystal surface, will vary with crystal face. Wetting will not therefore commence at all parts of the plate at the same time, and the recorded angle is the mean of several angles which operate round the sodium meniscus. There was visible evidence for this heterogeneous wetting, especially at the stage when wetting had just commenced.

Above 160°, the zinc phosphate film reacts on contact with sodium, and since the contact angle falls to below 20° within a few seconds of immersion (Fig. 1), this reaction is regarded as being completed almost immediately. A film of sodium phosphate will remain; since it is formed as a result of chemical reaction at the surface it may be less cohesive than the zinc phosphate film. The time (up to 10 min.) during which θ falls to 0° will represent the time required for the migration of zinc through this new film. The plot of log $(1/T_\theta)$ against $1/T$ for this temperature range indicates an activation energy of about 8 kcal.

Wetting of Untreated and Abraded Zinc Plates.—Zinc plates which were untreated (*i.e.*, not abraded or degreased, and exposed to the atmosphere for months) gave an initial contact angle near 180° in sodium at a temperature of 180°. This angle decreased to about 30° in 30 min., remained at that value for about 2 hr., and then increased slightly; the more incomplete is the wetting, the greater is the tendency for dewetting to occur on prolonged immersion. When similar plates were abraded with emery paper the final angle was 20°, and there was no evidence of dewetting. The capillary grooves on the surface caused by abrasion may contribute towards this rather lower contact angle.[3] When an abraded plate degreased for 6 hr. in hot acetone was used, θ was less than 30° within 30 sec., and decreased to 0° within 10 min. This behaviour is very similar to that observed with an electropolished degreased plate (Fig. 1), and there was again visual evidence of non-uniformity of wetting. Plates cleaned by reaction in aqueous hydrochloric acid or sodium hydroxide showed similar behaviour in sodium: wetting was not quite so rapid, θ reaching 0° in 15 min.

Some measurements upon abraded and degreased plates over a temperature range are given below:

Temperature	108°	108°	124°	175°
θ after 30 secs.	24°	39°	38°	18°
Time to reach $\theta = 0°$ (min.).....	9·0	10·0	10·0	8·0

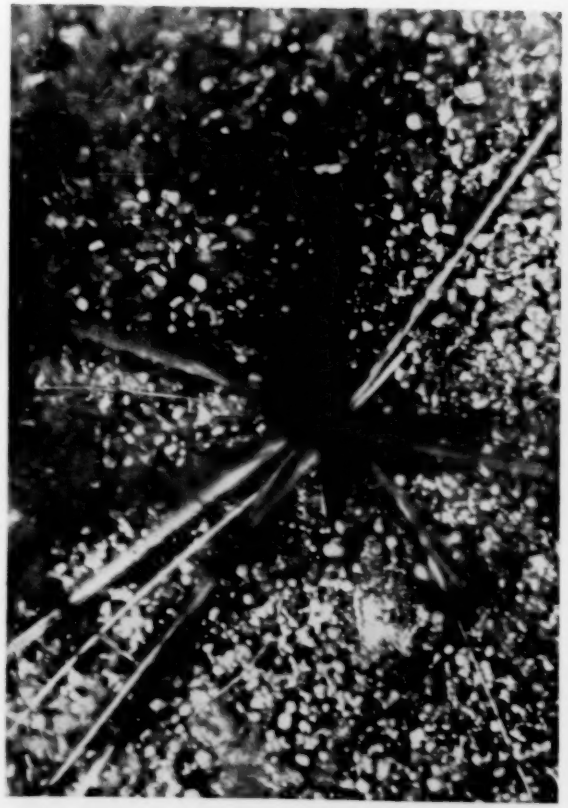
In this case the wetting time changes very little with temperature (in sharp contrast to the behaviour of the electropolished plates) and there is no evidence for a critical wetting temperature.

Mechanism of Wetting.—The difference in wetting behaviour between abraded and electropolished zinc results from the differing physical and chemical properties of zinc oxide and zinc phosphate films. By direct weighing, the thickness of the zinc oxide film on abraded, degreased zinc at room temperature has been shown to be 65 Å after 24 hr. and 90 Å after 100 hr.[23] Electron diffraction indicates that a single crystal of zinc in dry air at room temperature develops a film of zinc oxide 20—40 Å thick, which does not change appreciably during 16 days.[24] In the present experiments the zinc plates were abraded about 20 hr. before use, so that the zinc oxide film is probably less than 100 Å thick.

The reaction between sodium and zinc oxide shows no evidence for a critical reaction

[23] Vernon, Strand, and Akeroyd, *J. Inst. Metals*, 1939, **65**, 301.
[24] Raether, *J. Phys. Radium*, 1950, **11**, 11.

FIG. 3 (*a*).



Electropolished zinc : immersed at 168° for 130 min. (× 644.)

FIG. 3 (*b*).

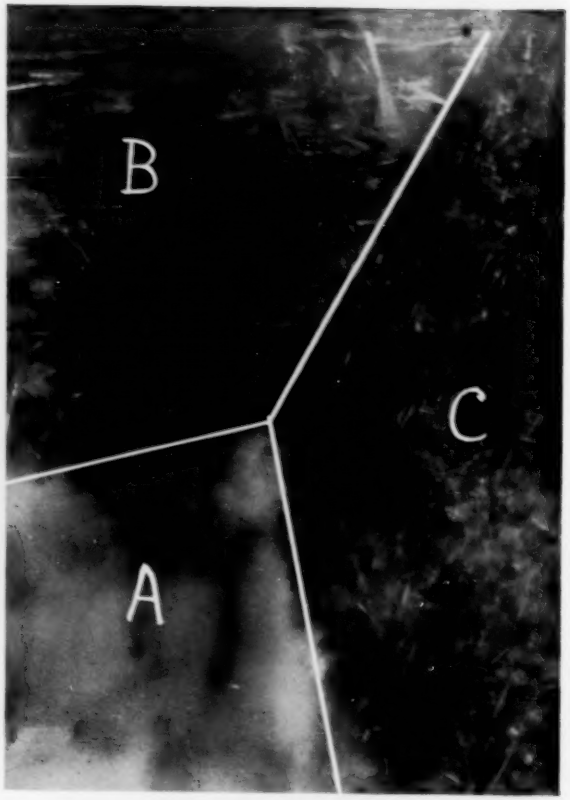
Abraded zinc : immersed at 180° for 80 min (× 644.)

[*To face Pt.* 1458.

Fig. 3 (*c*).

Abraded zinc : immersed at 168° for 30 min. (× 800.)

Fig. 3 (*d*).



Electropolished zinc : immersed at 130° for 150 min. (× 800.)

temperature. At 120° there was a slow reaction when a thin sintered zinc oxide block was immersed in sodium. The block became brown-black and changed to yellow on exposure to the atmosphere; this is attributed to sodium penetrated into the block. The reaction $ZnO + 2Na \longrightarrow Na_2O + Zn$ occurs with a decrease in free energy of 12 kcal.[25] The reaction proceeded a little more quickly with increase in temperature in the range 120—200°.

If the times required for complete wetting of electropolished plates above 160° (Fig. 1) are extrapolated towards 100°, they indicate times for wetting which are much longer than the 8—10 min. actually observed for abraded plates. The diffusion of zinc through the zinc oxide film can be the rate-determining step, and partial reaction of the film to give sodium oxide will not eliminate this factor, since sodium oxide has an extremely small solubility in sodium at these low temperatures.[26] The zinc oxide film is sufficiently thin for the Cabrera–Mott mechanism, which is inapplicable to the zinc phosphate films, to be important here; in this mechanism the directional movement of cations across the film is enhanced by the electrical field set up by electrons which have penetrated the film by the "tunnel" effect, and migration of zinc through the film would then be much more rapid than in the case of normal diffusion. The very small change in rate of wetting with temperature indicates an activation energy of much less than 1 kcal. This is in agreement with the activation energy (300 cal.) for the oxidation of zinc at room temperature,[23] which is again a process involving diffusion of zinc through very thin zinc oxide films.

Microscopical Examination of Zinc Surface after Wetting with Sodium.—Sodium was removed by washing in water, and the plates were dried with acetone and hot air. To the naked eye the plates had a mat grey surface, but under the microscope crystals were observed; photomicrographs (taken by using a Vickers Projection microscope) are shown in Fig. 3 (*a*)—(*d*). A completely wetted zinc surface, completely drained on withdrawal of the plate from liquid sodium, was covered with a mat of small granular crystals about 0·005 mm. across, but in places clumps of larger needle-shaped crystals up to 0·1 mm. long and 0·005 mm. wide occurred (Fig. 3*a*). Both crystals appear to consist of zinc metal. They have a bright, metallic appearance, which was unchanged when the plate was kept in a stoppered tube containing atmospheric air for six months, whereas the compound $Zn_{13}Na$ is grey and brittle, and reacts slowly with water and the atmosphere to give a coating of sodium hydroxide.[10] However, the phase diagram [10] indicates that the intermetallic compound, rather than zinc metal, crystallises from solution in sodium. We assume therefore that when the plates are washed in water, the compound $Zn_{13}Na$ reacts to leave zinc metal without major change in crystal form; zinc atoms in the compound are 4- or 5-valent, whereas the valency of sodium is 1—1·25.[12] Although the solubility of the compound in sodium is small,[10] the crystals are considered to be formed by a process of solution of the compound as first formed, and its redisposition in one or other of the crystalline forms, as the plate cools on each withdrawal from sodium. In areas where drainage is efficient, few clumps of needles are observed, but near the meniscus, or round an area of the plate not properly wetted, a ridge of liquid sodium is retained on the plate. More needles are then deposited, and the surface has the appearance shown in Fig. 3 (*b*).

Fig. 3 (*c*) shows the mat of small crystals (about 0·01 mm. long) which is obtained when the plate is wetted in either of two ways: by using either (*a*) high temperature and short immersion times (insufficient time has been allowed for the secondary process involving growth of large crystals at the expense of the small ones), or (*b*) long immersion times at low temperatures. In the latter case the velocity of both primary and secondary processes will be reduced. By using electropolished plates which were only partially wetted [Figs. 2 and 3 (*d*)], the non-uniformity of wetting can be related directly with the differing behaviour of the film covering the crystal faces. Fig. 3 (*d*) shows three separate crystals. Crystal A (not clear in the figure because of the necessarily shallow depth of focus) had resisted wetting; it was slightly etched, but retained the smooth surface formed by electropolishing. Crystals B and C had been wetted; the needles were mostly oriented in one direction, which varied with the crystal face involved.

[25] Osborne, *J. Metals* (Trans. A.I.M.E.) 1950, **188**, 600.
[26] "Liquid Metals Handbook," 2nd Edn., NAVEXOS P—733, p. 114; U.S. Govt. Printing Office, Washington 1952.

Experimental

Sodium.—The purification of sodium was described in Part I.[12]

Preparation of Zinc Plates.—" AnalaR " granulated zinc was melted in a silica crucible and cast in a steel mould to form a slab which was then machined to 0·5 mm. in thickness. Plates 2 cm. × 4 cm. were then cut from the sheet. Abrasion was carried out by rubbing with emery paper of decreasing coarseness (1—3/0), each grade being used in a direction at right angles to the previous one until all previous scratch marks were removed. Alkali-cleaned plates were boiled for 1 hr. in N-sodium hydroxide solution, then washed with water, alcohol, and ether. Acid-cleaned plates were immersed in 2N-hydrochloric acid for 30 sec., and washed as above. Plates were electropolished in a bath of 62·5% absolute alcohol and 37·5% syrupy phosphoric acid at room temperature,[25] a current density of 1·67 amp./sq. dm. at 2·6 volts being used. They were washed with water and acetone, and dried in hot air.

Preparation of Anhydrous Zinc Phosphate.—de Schulten's [26] method, which involves heating zinc phosphate tetrahydrate in boiling zinc chloride, followed by extraction of the latter with water and dilute acetic acid, could not be repeated; in each case the tetrahydrate was recovered, unchanged in analysis but in a different crystalline form. The anhydrous salt was prepared by heating the tetrahydrate in a silica boat for 3 hr. at about 900°. This gave a white sintered mass of the anhydrous salt, which fused on further heating. Weight loss on heating was 16·0% [Calc. for $Zn_3(PO_4)_2.4H_2O$: 15·75%]. Zinc was determined as zinc ammonium phosphate, and phosphate as ammonium phosphomolybdate [Found: Zn, 50·5; PO_4, 51·5. Calc. for $Zn_3(PO_4)_2$: Zn, 50·9; PO_4, 49·1%]. No trace of silicate was found in the product. The deviations in the analyses indicate some slight decomposition, probably with the formation of pyrophosphate. This occurs by sublimation of zinc oxide from the anhydrous salt, since loss of phosphoric acid from the hydrated salt during heating would give discrepancies in the reverse directions. The zinc phosphate blocks were degreased before use, in the same manner as the zinc plates, by extraction with acetone, the latter being then removed by heating the blocks in a stream of argon.

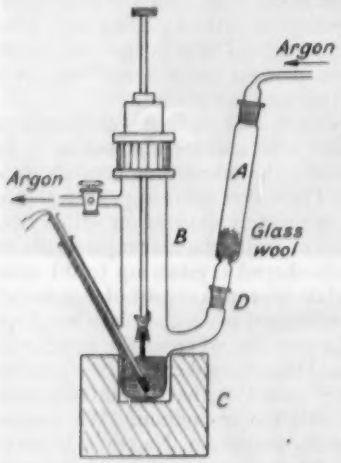


Fig. 4.

Zinc Oxide Blocks.—" AnalaR " zinc oxide was strongly compressed in a pellet screw press. The soft cylinders so obtained were cut to the desired shape, and heated for several hours at 1000°. The resulting ivory-coloured product was not friable.

Reaction of Sodium with Zinc Phosphate and Zinc Oxide.—A stream of argon (purified as described in Part I) was passed through the apparatus (Fig. 4) continuously during an experiment. Solid sodium in the filter tube *A* was melted by means of Electrothermal heating tapes. The liquid metal (about 10 ml.) was forced through the glass-wool filter plug in *A*, by pressure of argon, into the main tube *B*, which fitted closely into an electrically heated furnace *C*. The temperature was measured by immersing the thermocouple in the liquid metal. The block of reactant was attached, by crocodile clip, to the end of a brass rod which passed out of the tube, through a 1" vacuum coupling and a Wilson seal. During each experiment, the temperature was increased at the rate of about 0·5° per min. The block was withdrawn, observed, and reimmersed at two-minute intervals. At the end of each experiment the sodium was poured from *B* through the B14 joint *D* into a cold steel mould. It was then examined for reaction products.

Reaction Products with Zinc Phosphate and Zinc Oxide.—After reaction with zinc phosphate, the products contained in a large excess of sodium were treated with absolute alcohol. A grey-black alcohol-insoluble sludge remained, which gave a black powder on being shaken with water. This was metallic zinc, and all dissolved with effervescence in dilute hydrochloric acid. The aqueous extract contained sodium phosphate, and the quantities of sodium phosphate and zinc

[25] de Schulten, *Bull. Soc. chim.*, 1889, **1**, 472.
[26] Jacquet, *Métaux Corrosion Usure*, 1944, **19**, 71.
[26] de Schulten, *Bull. Soc. chim. France*, 1889, **2**, 300.

were respectively 96·5 and 82·5% of the theoretical yields. After reaction with zinc oxide, the excess of sodium was removed by absolute alcohol. A very small quantity of black powder remained which gave positive tests for zinc.

The authors thank the Director, Atomic Energy Research Establishment, Harwell, for financial assistance, and Mr. D. Rees for assistance with the radioactivity measurements.

THE UNIVERSITY, NOTTINGHAM. [*Received, October 26th*, 1955.]

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295. *The Occurrence of Triterpenes in the Aquifoliaceae and Ericaceae of Hong Kong.*

By H. R. ARTHUR, C. M. LEE, and C. N. MA.

Of the *Ilex* species endemic to the Colony, six contain ursolic acid, but *I. macrocarpa* contains oleanolic acid (the first report of it from this genus) and *I. pubescens* contains both acids; *Rhododendron farrerae* contains cerin, previously isolated only from cork, and *R. westlandii* contains a triterpenoid mixture which includes friedelin, *epi*friedelanol, and a new triterpene.

THE compounds reported below have been isolated from plants of Hong Kong during a search for new triterpenoid compounds.

The Aquifoliaceae of the Colony are confined to the genus *Ilex* of which ten species have been recorded. The leaves of the eight available species are being examined for the presence of triterpenoid compounds, which occur as mixtures in all species except *I. rotunda* from which ursolic acid was isolated without difficulty. Whilst ursolic acid has also been identified in *I. asprella*, *I. cinerea*, *I. hanceana*, *I. memecylifolia*, and *I. triflora*, it has been shown that *I. macrocarpa* contains oleanolic acid, and *I. pubescens* a mixture of both acids. Ursolic acid has been reported before in *Ilex* species [1] but this is the first report of oleanolic acid from this genus.

Regarding previous work carried out on the Ericaceae of the Colony, Arthur and Hui [2] showed that the leaves of all species contained ursolic acid and they [3] showed that the flavanone, matteucinol, was present in the leaves of *Rhododendron simsii*. Arthur [4] found that the leaves of *R. farrerae* contained the new flavanone, farrerol, but other species did not contain flavonoid compounds.

We report here that cerin (previously isolated only from cork [5]) occurs in the leaves of *R. farrerae* and that friedelin, *epi*friedelanol, and a new triterpene occur in a triterpenoid mixture from *R. westlandii*. Since the new triterpene occurs in very low yield and we will not be able to obtain more of it we record in the Experimental section what information we already possess.

EXPERIMENTAL

M. p.s of Aquifoliaceae compounds are corrected. All compounds have been characterised by mixed m. p. with authentic specimens. Analyses are by Dr. Zimmermann, Melbourne. Alumina used was B.D.H., analysis grade, and the light petroleum had b. p. 60—80°.

Aquifoliaceae.—The dried leaves of all Ilex species were extracted with ether. Crude triterpene acid was isolated from the ethereal extract as stated by Arthur and Hui [4] for the isolation of ursolic acid from the Ericaceae. Attempted fractional recrystallisation of the crude acid from ethanol or methanol gave for some species crystalline acid of sharp m. p. which was identified by derivatives; from other species crystalline material was not obtained. In those cases the crude triterpenoid mixtures were acetylated. Fractional recrystallisation then

[1] Nooyen, *Pharm. Weekblad*, 1920, **57**, 1128; Mendive, *J. Org. Chem.*, 1940, **5**, 235; Kariyone, Hashimoto, and Tobinaga, *J. Pharm. Soc. Japan*, 1953, **73**, 257; Kariyone, Hashimoto, and Kiguchi, *ibid.*, 1949, **81**, 313.
[2] Arthur and Hui, *J.*, 1954, 4683.
[3] *Idem*, *J.*, 1954, 2782.
[4] Arthur, *J.*, 1955, 3740.
[5] Chevreul, *Ann. Chim.*, 1815, **96**, 141.

afforded the pure acetates which on hydrolysis gave the acids which were identified as previously stated.

Samples of both acids gave in the Liebermann–Burchardt test a red ⟶ violet ⟶ blue ⟶ green colour. A sample of oleanolic acid was analysed (Found : C, 79·2; H, 10·7. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%) [acetate (Found : C, 77·1; H, 10·0; Ac, 7·6. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1; 1Ac, 8·8%)] and likewise a sample of ursolic acid (Found : C, 79·4; H, 10·7%) [acetate (Found : C, 77·7; H, 10·3%]. Other experimental results are summarised in the Table.

Plant	Acid	M. p. of acid (vac.)	M. p. of acetate	M. p. of Me ester	$[\alpha]_D$ * of acid	$[\alpha]_D$ † of acetate	Yield (%) crude acid (dry leaves)
I. asprella	Ursolic	286—288°	291—292°	—	—	+65°	0·03
I. cinerea	,,	286—288	291	—	+65°	—	1·06
I. hanceana	,,	285—288	289—290	—	—	+62	1·44
I. macrocarpa ...	Oleanolic	309—311	266—267	198° ‡	+76	—	1·32
I. memecylifolia...	Ursolic	285—286	286—287	—	—	+64	1·11
I. pubescens	,,	287—289	291—292	—	—	+66	0·58
,, ...	Oleanolic	309—310	264—266	—	—	—	0·10
I. rotunda	Ursolic	287—290	—	169	+66	—	1·67
I. triflora	,,	287—289	289—290	—	+66	—	—

* In MeOH–$CHCl_3$ (1 : 1). † In $CHCl_3$. ‡ Sinters at 107—112°.

Ericaceae.—(*a*) Rhododendron farrerae. Dried leaves (2 kg.) were extracted with ether (10 l.), and the ethereal extract was evaporated to dryness. The dark green residue was boiled repeatedly with methanol to remove ursolic acid and farrerol. The almost colourless methanol-insoluble fraction (8 g.) which remained was recrystallised several times from pyridine and then from benzene. Colourless needles of cerin, m. p. 256—258°, $[\alpha]_D^{26}$ −41·1° (*c* 0·71 in pyridine) (Found : C, 81·6; H, 11·5. Calc. for $C_{36}H_{56}O_3$: C, 81·4; H, 11·4%), were obtained. The infrared spectrum of this sample in the range 900—1350 cm.$^{-1}$ was identical with that of an authentic sample. On oxidation with chromic oxide in acetic acid cerin gave friedelindioic acid, m. p. 286—288° (decomp.; vac.) (Found : C, 76·3; H, 10·5. Calc. for $C_{36}H_{56}O_4$: C, 75·9; H, 10·6%), characterised as dimethyl ester, m. p. 176—177° (Found : C, 76·5; H, 10·9; OMe, 11·2. Calc. for $C_{32}H_{54}O_4$: C, 76·4; H, 10·8; 2OMe, 12·3%). Cerin was further characterised as the 2 : 4-dinitrophenylhydrazone, m. p. 254° (decomp.) (Found : N, 9·2. Calc. for $C_{36}H_{54}O_5N_4$: N, 9·0%), and oxime, m. p. 272—276° (Found : C, 78·6; H, 11·3; N, 2·8. Calc. for $C_{30}H_{51}O_2N$: C, 78·7; H, 11·2; N, 3·1%).

(*b*) Rhododendron westlandii. Dried leaves (11·5 kg.) were extracted with light petroleum at room temperature and the extract was concentrated in stages until coarse colourless crystals no longer separated. These crops were combined and recrystallised from chloroform, giving hexagonal plates (15 g.) of *epi*friedelanol, m. p. 277—278° (vac.) $[\alpha]_D^{23}$ −18·1° (*c* 0·99 in $CHCl_3$) (Found : C, 84·6; H, 12·3%. *M*, 425. Calc. for $C_{30}H_{52}O$: C, 84·0; H, 12·2%; *M*, 429). *epi*Friedelanol, which gave a pink ⟶ purple ⟶ brown colour in the Liebermann–Burchardt reaction, was characterised by conversion into the acetate (with pyridine and acetic anhydride), which separated from benzene in plates, m. p. 291—292° (vac.), $[\alpha]_D^{27}$ −45·0° (*c* 0·32 in $CHCl_3$) (Found : C, 82·0; H, 11·7. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%). The acetate resisted hydrolysis in boiling solutions of potassium hydroxide in ethanol and in ethylene glycol, and also in sulphuric–chromic acid, although the acetate group was shown to be present by infrared analysis. The benzoate (prepared with benzoyl chloride and pyridine) separated from benzene–methanol in plates, m. p. 251—252° (decomp.) (vac.), $[\alpha]_D^{22}$ −37·6 (*c*, 1·32 in $CHCl_3$) (Found : C, 83·4; H, 10·6. Calc. for $C_{37}H_{56}O_2$: C, 83·4; H, 10·6%). *epi*Friedelanol was converted into friedelindioic acid, m. p. 286° (decomp.), by chromic oxide in acetic acid, and in stabilised acetone (Bowers *et al.*[6]) into friedelin which separated from benzene in needles, m. p. 259—260° (vac.), $[\alpha]_D^{23}$ −27·3° (*c* 0·39 in $CHCl_3$) (Found : C, 84·6; H, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). Friedelin was characterised by conversion into friedelanol, m. p. 297—298° $[\alpha]_D^{28}$ −11·1° (*c* 0·07 in $CHCl_3$), by the method of Drake and Campbell[7] and into the 2 : 4-dinitrophenylhydrazone, m. p. 291° (decomp.; vac.) (Found : C, 71·4; H, 9·1; N, 9·3. Calc. for $C_{36}H_{54}O_4N_4$: C, 71·2; H, 9·0; N, 9·2%). epi*Friedelanol methyl ether* was prepared by boiling *epi*friedelanol (3·0 g.) with methyl iodide (500 ml.) and silver oxide for 35 hr. Recrystallisation from chloroform of the residue obtained after removal of methyl iodide yielded *epi*friedelanol. The chloroform mother-liquor was evaporated to dryness and the

[6] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

residue was dissolved in light petroleum and chromatographed over alumina, with benzene as eluant. Early fractions contained *epi*friedelanol but later fractions on recrystallisation from ethyl acetate deposited needles of the methyl ether, m. p. 219—220°, $[\alpha]_D^{21}$ −21·4° (*c* 0·49 in $CHCl_3$) (Found: C, 84·8; H, 12·0. $C_{31}H_{54}O$ requires C, 84·2; H, 12·3%).

The mother-liquor of the original petroleum extract from the plant after removal of *epi*friedelanol was concentrated and the colourless crystalline mixture (27 g.) which separated was collected and its light petroleum solution was chromatographed on alumina, light petroleum being used as eluant. The first fraction (0·1 g.) on recrystallisation from light petroleum deposited needles of a *substance*, m. p. 201—203°, $[\alpha]_D^{25}$ −80° (*c* 0·11 in $CHCl_3$) (Found: C, 85·1; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Like β-amyrin, this compound gave a deep red colour in the Liebermann–Burchardt test but it depressed the m. p. of the former by 32°, and was recovered unchanged after 4 hours' boiling in acetic anhydride and pyridine. It was isomerised by boiling ethanolic hydrochloric acid.

The second fraction (1·0 g.) from the column, obtained by elution with light petroleum–benzene (3 : 2), gave on recrystallisation from benzene needles of friedelin, m. p. 248—252°, $[\alpha]_D^{29}$ −27·5° (*c* 0·34 in $CHCl_3$) (Found: C, 84·6; H, 11·8. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%) [2 : 4-dinitrophenylhydrazone, m. p. 288° (decomp.; vac.) (Found: C, 71·6; H, 8·9; N, 9·7. Calc. for $C_{36}H_{54}O_4N_4$: C, 71·2; H, 9·0; N, 9·2%); oxime, m. p. 302—303° (decomp.; vac.) (Found: C, 81·4; H, 11·7; N, 3·4. Calc. for $C_{30}H_{51}ON$: C, 81·6; H, 11·7; N, 3·2%)].

The authors thank Professor J. E. Driver for his interest, Dr. A. R. Cole (University of Western Australia) for the infrared spectral analyses, Professors O. Jeger (Eidg. Technische Hochschule, Zürich) and E. J. Corey (University of Illinois), and Drs. D. E. White (University of Western Australia) and R. M. Gascoigne (University of Technology, Sydney) for authentic samples of some of the triterpenes, Mr. H. C. Tang (Government Herbarium, Hong Kong) for the identification of plant material, and Mr. S. C. Chan for preparing cerin oxime.

University of Hong Kong. [*Received, December 1st, 1955.*]

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296. *Homolytic Aromatic Substitution. Part XI.* The Phenylation of Toluene, Ethylbenzene, and isoPropylbenzene.*

By D. H. Hey, B. W. Pengilly, and Gareth H. Williams.

Partial rate factors are determined for the phenylation of ethylbenzene and *iso*propylbenzene by an analysis of the products formed in the competitive phenylation of mixtures of them with (*a*) nitrobenzene and (*b*) pyridine. The proportions of the isomers formed in the nuclear phenylation, and the relative amounts of the products derived from nuclear and side-chain attack, are determined by infrared spectroscopy. The partial rate factors for ethylbenzene are similar to those for toluene, and those for *iso*propylbenzene are similar to those for *tert.*-butylbenzene, the determination of which has been reported previously. The existence of a steric effect which inhibits substitution *ortho* to an *iso*propyl group is thus revealed. A reinvestigation of the by-products of the phenylation of toluene shows the presence of a little dibenzyl, resulting from attack in the side-chain, and necessitates a small modification of the partial rate factors previously reported for the phenylation of toluene. The theoretical significance of these results is discussed.

The analysis of the products obtained in the reactions of benzoyl peroxide with *tert.*-butylbenzene and with toluene, and the determination of the partial rate factors for the phenylation of these compounds, was reported in Parts VII and VIII of this series.[1] In addition, the possibility of attack on the side-chains of alkylbenzenes was briefly discussed. The absence of α-hydrogen atoms in the side-chain of *tert.*-butylbenzene, and their low reactivity in the side-chain of toluene, results in very little attack on the side-chain of toluene and none on that of *tert.*-butylbenzene when benzoyl peroxide is allowed to

* Part X, *J.*, 1955, 3963.

[1] (*a*) Cadogan, Hey, and Williams, *J.*, 1954, 3352; (*b*) Hey, Pengilly, and Williams, *J.*, 1955, 6.

decompose in solutions in these solvents. The side-chain of ethylbenzene and of *iso*propylbenzene, on the other hand, is known to be much more susceptible to free-radical attack than that of toluene. This attack takes the form of the abstraction of an α-hydrogen atom, and the subsequent dimerisation of the radicals so formed. These radicals are, like the benzyl radical, considerably stabilised by resonance, and their consequently low reactivity is demonstrated by their inability to effect substitution at aromatic nuclei. They are, apparently, sufficiently stable to exist in solution in concentrations high enough to enable dimerisation to take place. This property of radicals analogous to benzyl is well known and, indeed, the production of 2 : 3-dimethyl-2 : 3-diphenylbutane (dicumyl) from *iso*propylbenzene has long been regarded as a test for the incidence of homolytic mechanisms.[2]

Thus it is apparent that a complete account of the phenylation of these two hydrocarbons requires a knowledge of the reactivity of the side-chains compared with that of the nuclei, as well as the specification of the reactivities of the nuclear positions in terms of partial rate factors. Measurements are therefore reported in the present communication of the relative amounts of the products derived from side-chain and nuclear attack, the ratios of the amounts of the products derived from substitution at the various nuclear positions, and the reactivities of the compounds towards nuclear attack compared with standard compounds, nitrobenzene and pyridine. In this manner, complete specifications of the reactivity of ethylbenzene and *iso*propylbenzene towards attack by phenyl radicals become possible and comparisons can be made among the members of the series of alkylbenzenes in order to discover the effects of various alkyl groups on homolytic reactivity.

The first of the above determinations, namely, that of the relative amounts of side-chain and nuclear attack, is of significance only if the side-chain and nuclear reactions are of the same kinetic order, for, if they are not, the amount of side-chain attack must depend on the concentration of benzoyl peroxide. The non-dependence of the relative amounts of side-chain and nuclear attack on the concentration of benzoyl peroxide is demonstrated for the case of *iso*propylbenzene, where the same result was obtained from solutions of different concentration. It is also demonstrated (see below) that the radical which attacks the side-chain is phenyl, and thus the nuclear and side-chain reactions with, for example, *iso*propylbenzene, can be represented by schemes (1) and (2) respectively.

$$C_6H_5\cdot CHMe_2 + Ph\cdot \longrightarrow Ph\cdot C_6H_4\cdot CHMe_2 + H\cdot \quad \ldots\ldots (1)$$

$$\left.\begin{aligned} C_6H_5\cdot CHMe_2 + Ph\cdot &\longrightarrow C_6H_5\cdot CMe_2\cdot + PhH \\ 2C_6H_5\cdot CMe_2\cdot &\longrightarrow C_6H_5\cdot CMe_2\cdot CMe_2\cdot C_6H_5 \end{aligned}\right\} \quad \ldots\ldots (2)$$

The application of the " steady-state " treatment to scheme (2) reveals that it obeys the same kinetic law as that which governs scheme (1), namely, that the rate of formation of the products is proportional to the concentrations of *iso*propylbenzene and the phenyl radical.

In addition to the products of nuclear and side-chain attack, some acetophenone is formed in the reactions, presumably by oxidation of ethylbenzene and *iso*propylbenzene. The oxidising agent in this side-reaction is not benzoyl peroxide, because almost all the peroxide used is accounted for by the amounts of the products formed from nuclear and side-chain attack. The oxidising agent is therefore probably oxygen, since the reactions were not conducted in an inert atmosphere. The aerial oxidation of ethylbenzene has been discussed by Emerson, Heyd, Lucas, Cook, Lyness, and Stevenson,[3] who suggested that 1-phenylethyl hydroperoxide $C_6H_5\cdot CH(O\cdot OH)\cdot CH_3$ was first formed, and that this decomposed thermally into two free radicals (1-phenylethoxy and hydroxyl), either of which, by subsequent reaction with more ethylbenzene, could lead to the formation of acetophenone. The formation of acetophenone by the atmospheric oxidation of *iso*propylbenzene has been noted on a number of occasions (see, for example, Pines, Kvetinskas, and Ipatieff[4]), and is believed to proceed in an analogous manner.

In a recent report by Rondestvedt and Blanchard[5] of the phenylation of toluene,

[2] Kharasch, McBay, and Urry, *J. Org. Chem.*, 1945, **10**, 401.
[3] Emerson, Heyd, Lucas, Cook, Lyness, and Stevenson, *J. Amer. Chem. Soc.*, 1948, **70**, 3764.
[4] Pines, Kvetinskas, and Ipatieff, *J. Amer. Chem. Soc.*, 1955, **77**, 343.
[5] Rondestvedt and Blanchard, *ibid.*, p. 1769.

ethylbenzene, and *iso*propylbenzene, the presence of dibenyl and of a small amount of an unidentified substance believed to be diphenyl (or diphenylmethane) in the product of the reaction of benzoyl peroxide with toluene, is reported. This is now confirmed by a re-investigation of the by-products of this reaction.

Experimental Methods and Results

Preparation of Reagents.—Unless otherwise stated, the light petroleum used had b. p. 60—80°, and all solids were recrystallised to constant m. p.

Benzoyl peroxide (May and Baker), nitrobenzene, and pyridine were purified according to the procedures described in Part II,[6] and nitromethane according to that described in Part IV.[7] Ethylbenzene and *iso*propylbenzene (B.D.H.) were washed with concentrated sulphuric acid until the washings were colourless, then with aqueous sodium hydrogen carbonate, and with water, and dried ($MgSO_4$); the pure hydrocarbons were obtained after distillation from sodium through a 6-foot, helix-packed column (b. p.s 136°/760 mm. and 152°/760 mm. respectively). Specimens of 2-ethyl-, 3-ethyl-, and 2-*iso*propyl-diphenyl were kindly supplied by Drs. I. A. Goodman and P. H. Wise of the National Advisory Committee for Aeronautics at the Lewis Flight Propulsion Laboratory, Cleveland, Ohio, U.S.A. 4-Ethyldiphenyl was prepared from 4-acetyldiphenyl, which was prepared by Ferriss and Turner's method [8] from acetyl chloride and diphenyl. The 4-acetyldiphenyl (2·6 g.) was reduced by Huang-Minlon's modification [9] of the Wolff–Kishner method; it was heated with potassium hydroxide (2·5 g.), hydrazine hydrate (1·8 ml.), and ethylene glycol (18 ml.) on a metal-bath at 230°, and water and hydrazine hydrate were distilled off until the temperature of the liquid reached 190°. The mixture was maintained under reflux for 2 hr., then allowed to cool. It was extracted with ether and the extracts were dried (Na_2SO_4). Evaporation of the ethereal extract and distillation yielded colourless, crystals, b. p. 74°/10 mm. (1·85 g.). These crystallised from aqueous methanol yielding 4-ethyldiphenyl, m. p. 35° (Mowry, Renoll, and Huber [10] reported m. p. 34—35°). 4-*iso*Propyldiphenyl was prepared by heating *p*-*iso*propylbenzoic acid (Eastman-Kodak) under reflux with thionyl chloride, and the acid chloride so formed was distilled; it had b. p. 138°/22 mm. This was used to prepare di-*p*-*iso*propylbenzoyl peroxide by Hey and Walker's method.[11] The peroxide [m. p. 89° after crystallisation from methanol (Cooper [12] reports m. p. 98°); 6 g.] was allowed to decompose in benzene (500 ml.) at 80°, and the product was worked up by the standard procedure (Part II[6]). Distillation yielded 4-*iso*propyldiphenyl, b. p. 134°/3 mm.; this oil was further purified by fractional freezing, to give pure 4-*iso*propyldiphenyl (2·9 g.), m. p. 11° (Found: C, 91·6; H, 8·4. Calc. for $C_{15}H_{16}$: C, 91·8; H, 8·2%). Rondestvedt and Blanchard [5] reported b. p. 110—112°/1 mm., n_D^{20} 1·5831 for 4-*iso*propyldiphenyl.

3-Nitrodiphenyl [13] was reduced catalytically in benzene solution with hydrogen at 1 atm. in the presence of Raney nickel. The amine was obtained as the hydrochloride (93%). 3-Iododiphenyl was prepared from 3-aminodiphenyl hydrochloride by diazotisation with sodium nitrite and reaction of the diazonium salt solution with potassium iodide. It was obtained as a pale yellow solid, m. p. 25°, b. p. 146°/1·5 mm., in 57% yield. Cadogan, Hey, and Williams [14] reported m. p. 26·5°.

3-*iso*Propyldiphenyl was prepared from 3-*iso*propenyldiphenyl, which was prepared by Mowry, Dazzi, Renoll, and Shortridge's method [14] by adding 3-iododiphenyl (22·4 g.) in dry ether (46 ml.) slowly to magnesium turnings (1·94 g.) and ether (46 ml.) in a flask equipped with a stirrer and a double-surface condenser. Initiation of the reaction proved difficult, but was effected by a trace of ethylmagnesium bromide. When addition of the 3-iododiphenyl was complete, the mixture was boiled under reflux for 1 hr. A mixture of dry (K_2SO_4) acetone (7 ml.) and ether (35 ml.) was then added at such a rate as to maintain gentle boiling. The mixture was allowed to boil under reflux overnight. Saturated aqueous ammonium chloride (50 ml.) was then added with stirring, and when hydrolysis was complete, the aqueous layer was extracted several times with ether, and the extracts were combined with the main ethereal layer.

[6] Augood, Hey, and Williams, *J.*, 1952, 2094.
[7] Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412.
[8] Ferriss and Turner, *J.*, 1920, 1140.
[9] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[10] Mowry, Renoll, and Huber, *ibid.*, p. 1105.
[11] Hey and Walker, *J.*, 1948, 2213.
[12] Cooper, *J.*, 1951, 3106.
[13] Elks, Haworth, and Hey, *J.*, 1940, 1284.
[14] Mowry, Dazzi, Renoll, and Shortridge, *J. Amer. Chem. Soc.*, 1948, **70**, 1916.

Evaporation of the ether yielded impure 2-(3-diphenylyl)propan-2-ol (18·5 g.). The crude alcohol was boiled under reflux with acetic anhydride (19·5 ml.) for 3 hr. After removal of the acetic acid and the excess of anhydride by fractional distillation under reduced pressure, the product was carefully fractionated. The first fraction (b. p. 135—150°/14 mm.) consisted of diphenyl, and the second (b. p. 160—177°/14 mm.) of crude 3-*iso*propenyldiphenyl. This was redistilled, yielding 3-*iso*propenyldiphenyl, b. p. 167—170°/14 mm. (3·8 g.) (Mowry, Dazzi, Renoll, and Shortridge[14] reported b. p. 160—161°/12 mm.). 3-*iso*Propenyldiphenyl (3·8 g.) in glacial acetic acid (30 ml.) was hydrogenated catalytically with Adams catalyst (0·1 g.) and the theoretical quantity of hydrogen at room temperature and atmospheric pressure. The product was distilled three times, yielding 3-*iso*propyldiphenyl, b. p. 80°/ 0·1 mm., n_D^{20} 1·5765 (3·5 g.) (Found : C, 91·4; H, 8·4. Calc. for $C_{15}H_{16}$: C, 91·8; H, 8·2%) (Rondestvedt and Blanchard [5] reported b. p. 110—115°/1·3 mm., n_D^{25} 1·5807).

2 : 3-Dimethyl-2 : 3-diphenylbutane (tetramethyldibenzyl, dicumyl) was prepared from *iso*propylbenzene and acetyl peroxide (Kharasch, McBay, and Urry [3]). An ethereal solution of acetyl peroxide was prepared by Gambarjan's method.[15] Ice (35 g.) was added slowly to a stirred mixture of acetic anhydride (18 g.), ether (100 ml.), and sodium peroxide (10 g.) at −15°. When the temperature reached 0° the mixture was kept at this temperature for 2 hr. and the ethereal layer decanted off. Calcium chloride was added to the ethereal layer and the mixture set aside overnight at 0°. After filtration, the ether was removed from the filtrate by gentle suction at room temperature, while a little *iso*propylbenzene was added to ensure that no crystalline acetyl peroxide was deposited. The resulting solution was added dropwise to well-stirred *iso*propylbenzene (250 ml.) on a steam-bath. After the addition was complete the excess of *iso*propylbenzene, together with the acetic acid formed, was removed by distillation, and the residue distilled under reduced pressure. The fraction of b. p. 125—128°/0·7 mm. consisted of crude 2 : 3-dimethyl-2 : 3-diphenylbutane (2 g.), which crystallised from methanol in needles, m. p. 118° (Kharasch, McBay, and Urry [3] reported m. p. 115°).

2 : 3-Diphenylbutane, in both its racemic and its *meso*-form, was prepared by a similar reaction with ethylbenzene and acetyl peroxide at 100°. The product was distilled at 0·5 mm., and racemic and *meso*-2 : 3-diphenylbutane were separated by treatment of the mixture with methanol, in which the *meso*-form is almost insoluble. The methanolic solution of racemic 2 : 3-diphenylbutane was distilled, and the fraction of b. p. 114—118°/2 mm. was twice redistilled, yielding racemic 2 : 3-diphenylbutane as a colourless oil (b. p. 116°/2 mm., n_D^{23} 1·5495). Kharasch, McBay, and Urry [3] reported b. p. 106°/2 mm., n_D^{20} 1·5517, for this form. The *meso*-2 : 3-diphenylbutane was purified by crystallisation (m. p. 128°) from nitromethane (Kharasch, McBay, and Urry [3] reported m. p. 123—125°).

Determination of the Extent of Side-chain Attack and the Ratio of the Isomeric Ethyldiphenyls formed in the Phenylation of Ethylbenzene.—Benzoyl peroxide (6 g.) was allowed to decompose in ethylbenzene (214 ml.) in a thermostat at 80° for 80 hr. When the reaction was complete free benzoic acid was removed by extraction with saturated sodium hydrogen carbonate solution. The mixture was then worked up by the standard procedure described in Part II.[9] In Expt. 3, carbon tetrachloride (60 ml.) was added to the mixture after reaction, and the lowest-boiling fraction (b. p. 78—80°) from the first distillation, containing carbon tetrachloride and any benzene formed in the reaction, was collected separately. This fraction was treated with a mixture of concentrated sulphuric acid (10 ml.) and fuming nitric acid (10 ml.), dropwise with shaking at room temperature. When addition was complete the mixture was refluxed for ¼ hr. and poured on ice (25 g.). The crystalline product formed was filtered off, washed with water, and dried. Crystallisation from aqueous ethanol gave *m*-dinitrobenzene (0·87 g.), m. p. and mixed m. p. 90°. This is equivalent to 0·40 g. of benzene. The diaryl fraction from Expt. 2 was carefully distilled under reduced pressure into two fractions. The second fraction, b. p. 70—100°/0·2 mm., consisted of a mixture of diaryls. The first fraction, b. p. 20—60°/0·3 mm. (1·5 g.), which was shown by infrared analysis not to contain any ethyldiphenyls or 2 : 3-diphenylbutane, was identified as acetophenone (semicarbazone, m. p. and mixed m. p. 201—202°). The diaryl fractions from expts. 1 and 3 were treated with sodium hydrogen sulphite solution to remove any acetophenone present.

In each reaction a high-boiling residue was left after separation of the diaryl fraction by distillation. This residue was assumed to consist of ethylterphenyls and products arising from the phenylation of, and abstraction of hydrogen from, 2 : 3-diphenylbutane. The results of these reactions are summarised in Table 1.

[15] Gambarjan, *Ber.*, 1909, **42**, 4003.

TABLE 1. *Products obtained in the phenylation of ethylbenzene.*

Experiment	1	2	3
Diaryl fraction (b. p. 70—100°/0·2 mm.) (g.)	2·373	2·419	2·385
Residue (b. p. >120°/0·3 mm.) (g.)	1·485	1·538	1·670
Free $Ph{\cdot}CO_2H$ (g.)	1·53	1·35	1·43
$Ph{\cdot}CO_2H$ from hydrolysis of esters (g.)	0·57	0·55	0·49
Total $Ph{\cdot}CO_2H$ (g.)	2·10	1·90	1·92
Benzoyl peroxide accounted for (neglecting residues) (%)	79	76	75·5

meso-2 : 3-Diphenylbutane was separated from the other compounds present in the diaryl fraction (racemic 2 : 3-diphenylbutane and 2-, 3-, and 4-ethyldiphenyl) by fractional crystallisation from nitromethane, in which *meso*-2 : 3-diphenylbutane is only sparingly soluble. Its identity was confirmed by its m. p. and mixed m. p. (128°). The weights of *meso*-2 : 3-diphenylbutane obtained from experiments 1, 2, and 3 were 0·532, 0·545 and 0·536 g. respectively.

Spectrographic analysis of the diaryl fractions after treatment with nitromethane was carried out with a Grubb-Parsons single-beam instrument fitted with an automatic pen-recorder. Nitromethane was used as solvent, since it has no bands in the range 11—15 mμ, where the characteristic bands of the ethyldiphenyls occur. The spectra were recorded by using a 130 mμ rock-salt cell with a speed of wave-length scanning and slit opening such that the energy of transmission recorded for the pure solvent was nearly constant over the required range. Calibration spectra were recorded for 2-, 3-, and 4-ethyldiphenyl and for *meso*- and racemic 2 : 3-diphenylbutane, and measurements on the spectra of mixtures for analysis made at the following characteristic absorption maxima : 2-ethyldiphenyl, 747 $cm.^{-1}$; 3-ethyldiphenyl, 806 $cm.^{-1}$; 4-ethyldiphenyl, 842 $cm.^{-1}$. These measurements enabled the concentrations of these isomerides to be calculated. The concentration of racemic 2 : 3-diphenylbutane was then obtained by difference. The accuracy of the determinations was tested by preparing mixtures of the three ethyldiphenyls and racemic 2 : 3-diphenylbutane in known concentration in nitromethane. These were analysed by the infrared method and the results obtained are given in Table 2.

TABLE 2. *Analysis of mixtures of ethyldiphenyls and racemic* 2 : 3-*diphenylbutane.*

	Solution S1		Solution S2	
	Known composition (%)	Composition found (%)	Known composition (%)	Composition found (%)
2-Ethyldiphenyl	41	41	23	21
3- ,,	10	12	30	33
4- ,,	6	7	17	17
Racemic 2 : 3-diphenylbutane	43	40	30	29

The analyses of the products from reactions 1, 2, and 3 are reported in Table 3. Dannley and Zaremsky [16] have reported the formation of 50% of 2-, 25% of 3-, and 25% of 4-ethyldiphenyl in the phenylation of ethylbenzene with benzoyl peroxide.

The results on the composition of the products, calculated from the data contained in Table 3, together with the weights of *meso*-2 : 3-diphenylbutane, are given in Table 4.

TABLE 3. *Spectrographic analyses of product of phenylation of ethylbenzene.*

	Composition (% by weight)			
Expt.	2-Ethyldiphenyl	3-Ethyldiphenyl	4-Ethyldiphenyl	Racemic 2 : 3-diphenylbutane
1	37·8	18·8	13·5	29·9
2	37·5	19·8	13·4	29·3
3	36·6	19·7	14·0	29·7

TABLE 4. *Composition of the product of reaction of ethylbenzene with benzoyl peroxide.*

Expt.	Nuclear attack (% by wt.)	Side-chain attack (% by wt.)	Composition of products of nuclear attack (% by wt.)		
			2-Ethyldiphenyl	3-Ethyldiphenyl	4-Ethyldiphenyl
1	44	56	54	27	19
2	46	54	53	28	19
3	46	54	52	28	20
Mean	45	55	53	28	19

Determination of the Extent of Side-chain Attack and the Ratio of Isomeric iso*Propyldiphenyls formed in the Phenylation of* iso*Propylbenzene.*—In expt. 4, benzoyl peroxide (6 g.) was allowed to

decompose in *iso*propylbenzene (226 ml.) in a thermostat at 80° for 72 hr. In expts. 5 and 6, benzoyl peroxide (10 g.) and *iso*propylbenzene (150 ml.) were used. Mixture 7 was the neutral fraction of the product of expt. 14 (see below), one of the pyridine–*iso*propylbenzene competitive reactions. After the reactions were complete the mixtures were worked up by the standard procedure, except that in expt. 4 free benzoic acid was removed as described for the reactions with ethylbenzene, and benzene was estimated as described for the reaction with ethylbenzene and found to be 1·2 g. The determination of acetophenone was also carried out on this mixture, and 1·25 g. were isolated and identified as the semicarbazone (m. p. and mixed m. p. 201—202°). Since the diaryl fractions were solid, they clearly contained material other than the *iso*propyldiphenyls, as these are all liquids. Careful treatment of these fractions with nitromethane was therefore employed in order to separate them into 2 : 3-dimethyl-2 : 3-diphenylbutane (dicumyl) (m. p. and mixed m. p. 119°) and liquid fractions the analyses of which corresponded closely with that calculated for *iso*propyldiphenyl (Found : C, 91·6; H, 8·4. Calc. for $C_{15}H_{16}$: C, 91·8; H, 8·2%), and which was found by spectrographic analysis to contain only a small amount of 2 : 3-dimethyl-2 : 3-diphenylbutane. The results of these reactions are summarized in Table 5.

TABLE 5. *Products obtained in the phenylation of* iso*propylbenzene.*

Experiments :	4	5	6	7
Diaryl fraction (b. p. 60—120°/0·1 mm.) (g.)	3·303	4·650	4·666	1·657
Residue (b. p. >120°/0·1 mm.) (g.)	1·631	2·366	2·217	—
Dimethyldiphenylbutane removed from diaryl fraction (g.)	1·801	2·538	2·195	0·807
Free $Ph{\cdot}CO_2H$ (g.)	1·55	—	—	—
$Ph{\cdot}CO_2H$ from hydrolysis of esters (g.)	0·28	—	—	—
Total $Ph{\cdot}CO_2H$ (g.)	1·83	3·40	3·38	—
Benzoyl peroxide accounted for (neglecting residue) (%)	75	72·5	69	—

The spectrographic analysis of the diaryl fractions after treatment with nitromethane was carried out by the method used for the reactions with ethylbenzene. Calibration spectra were recorded for 2-, 3-, and 4 *iso*propyldiphenyl and for 2 : 3-dimethyl-2 : 3-diphenylbutane, and measurements on the mixtures for analysis were made at the following frequencies : 2-*iso*propyldiphenyl, 751 cm.$^{-1}$; 3-*iso*propyldiphenyl, 803 cm.$^{-1}$; 4-*iso*propyldiphenyl, 841 cm.$^{-1}$. The concentration of 2 : 3-dimethyl-2 : 3-diphenylbutane was obtained by difference. The accuracy of the determinations was tested by the analysis of known mixtures of the three *iso*propyldiphenyls and 2 : 3-dimethyl-2 : 3-diphenylbutane. These results are given in Table 6.

TABLE 6. *Analysis of mixtures of* iso*propyldiphenyls and* 2 : 3-*dimethyl-2 : 3-diphenylbutane.*

	Solution S3		Solution S4	
	Known composition (%)	Composition found (%)	Known composition (%)	Composition found (%)
2-*iso*Propyldiphenyl	28	25	39	41
3- ,,	40	39	30	30
4- ,,	22	24	16	18
2 : 3-Dimethyl-2 : 3-diphenylbutane	10	12	15	11

TABLE 7. *Spectrographic analysis of product of phenylation of* iso*propylbenzene.*

	Composition (% by weight)			
Experiment	2-*iso*Propyldiphenyl	3-*iso*Propyldiphenyl	4-*iso*Propyldiphenyl	2 : 3-Dimethyl-2 : 3-diphenylbutane
4	25·8	33·0	22·4	18·8
5	27·0	37·6	23·7	11·7
6	25·1	36·3	21·8	16·8
7	26·4	33·8	22·6	17·2

The analyses of the products from reactions 4, 5, 6, and 7 are reported in Table 7. Dannley and Zaremsky [16] have reported the formation of 10% of 2-, 60% of 3-, and 30% of 4-*iso*propyldiphenyl, and Rondestvedt and Blanchard [5] 29%, 50%, and 21% respectively, in the phenylation of *iso*propylbenzene.

The results of the composition of the products calculated from the data contained in Table 7, together with the weights of 2 : 3-dimethyl-2 : 3-diphenylbutane removed in treatment with nitromethane (Table 5), are given in Table 8.

[16] Dannley and Zaremsky, *J. Amer. Chem. Soc.*, 1955, **77**, 1588.

TABLE 8. *Composition of the product of reaction of* iso*propylbenzene with benzoyl peroxide.*

Experiment	Nuclear attack (% by wt.)	Side-chain attack (% by wt.)	Composition of products of nuclear attack (% by wt.) 2-*iso*Propyldiphenyl	3-*iso*Propyl diphenyl	4-*iso*Propyl diphenyl
4	37	63	31·8	40·7	27·5
5	40	60	30·5	42·5	27·0
6	38·5	61·5	30·2	43·6	26·4
7	42	58·5	31·8	40·8	27·4
Mean	39·5	60·5	31	42	27

In view of the excellent agreement between the results of expts. 4—7, and the satisfactory results obtained in the analyses of synthetic mixtures (Table 6), the present results are considered to be more accurate than those of the earlier workers. A similar assessment may be applied to the results obtained with ethylbenzene (Tables 2 and 4).

Determination of $^{PhEt}_{PhNO_2}K$.—Benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of ethylbenzene and nitrobenzene in a thermostat at 80° for 72 hr. The mixture was then worked up by the procedure described in Part VIII [15] for competitive experiments with mixtures of nitrobenzene and toluene. As in those experiments, three fractions—the pre-forerun, the forerun, and the diaryl fraction—were retained from the final distillation. All three fractions were analysed for the nitro-group by titration with titanous chloride and, as a check, for nitrogen by the micro-Dumas method. The pre-forerun (~3 g., b. p. 96°/20 mm.) consisted of pure nitrobenzene, thus showing that no ethyldiphenyls had been lost in the distillation. The forerun (b. p. 30—80°/0·1 mm) consisted of nitrobenzene together with some of the ethyldiphenyls. It may be safely assumed that the forerun contained no nitrodiphenyls, since these were found not to distil until a temperature 40° above that at which the forerun was collected had been reached. The diaryl fraction (b. p. 80—130°/0·1 mm.) consisted of ethyldiphenyls, nitrodiphenyls, and *meso*- and racemic 2 : 3-diphenylbutane. The residue in the flask after distillation amounted to less than 10% of the diaryl fraction and consisted mainly of tar not removed on the alumina column. The results of these competitive experiments are summarised in Table 9.

TABLE 9.

Experiment :	8	9
Diaryl fraction (g.)	1·783	1·805
$Ph{\cdot}C_6H_4{\cdot}NO_2$ in diaryl fraction (%)	70·9	73·7
Forerun (g.)	2·537	2·147
N in foreruns (%)	9·95	9·60
Hydrocarbons in forerun (g.)	0·312	0·338
$Ph{\cdot}C_6H_4{\cdot}NO_2$ (g.) in diaryl fraction	1·264	1·331
Corr. wt. of diaryl fraction (g.)	2·095	2·143
Total hydrocarbons (g.)	0·831	0·812
$Ph{\cdot}C_6H_4{\cdot}C_2H_5$ (g.)	0·374	0·365
Free $Ph{\cdot}CO_2H$ (g.)	2·82	2·80
$Ph{\cdot}CO_2H$ from hydrolysis of esters (g.)	0·50	0·50
Benzoyl peroxide accounted for (%)	84	82
$^{PhEt}_{PhNO_2}K$	0·32	0·30

Hence $^{PhEt}_{PhNO_2}K = 0{\cdot}31$

The sum of the weights of 2-, 3-, and 4-ethyldiphenyl formed was obtained from the total weight of hydrocarbon by correcting for side-chain attack, using the data given in Table 4.

Determination of $^{Ph\text{-}iso\text{-}Pr}_{PhNO_2}K$.—In expts. 10 and 11, benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of *iso*propylbenzene and nitrobenzene in a thermostat at 80° for 72 hr. The mixtures were then worked up and analysed by the procedure described above for the determination of $^{PhEt}_{PhNO_2}K$. The results of these experiments are summarised in Table 10.

The sum of the weights of 2-, 3-, and 4-*iso*propyldiphenyl formed was obtained from the total weight of hydrocarbon by correcting for side-chain attack from the data given in Table 8.

Determination of $^{PhEt}_{PyH}K$ and $^{Ph\text{-}iso\text{-}Pr}_{PyH}K$.—In expts. 12 and 13, benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of ethylbenzene and pyridine. In expts. 14 and 15, the same weight of benzoyl peroxide was allowed to decompose in an equimolar mixture (200 ml.) of *iso*propylbenzene and pyridine. The products were worked up and

separated into neutral and basic fractions as described in Part VIII.[15] The results of these experiments are summarised in Tables 11 and 12.

TABLE 10.

Experiment:	10	11
Diaryl fraction (g.)	2·537	2·153
$Ph{\cdot}C_6H_4{\cdot}NO_2$ in diaryl fraction (%)	66·5	71·7
Forerun (g.)	0·547	0·81
N in forerun (%)	9·75	8·05
Hydrocarbons in forerun (g.)	0·079	0·237
Corr. wt. of diaryl fraction (g.)	2·616	2·390
$Ph{\cdot}C_6H_4{\cdot}NO_2$ in diaryl fraction (g.)	1·689	1·543
Total hydrocarbons (g.)	0·927	0·847
$Ph{\cdot}C_6H_4{\cdot}Pr^i$ (g.)	0·366	0·335
$Ph{\cdot}CO_2H$ (g.)	3·3	3·4
Benzoyl peroxide accounted for (%)	86	85
$^{PhisoPr}_{PhNO_2}K$	0·215	0·220

Hence $^{PhisoPr}_{PhNO_2}K = 0{\cdot}217$

TABLE 11.

Experiment:	12	13
Phenylpyridines (g.)	0·603	0·529
Neutral diaryl fraction (g.)	1·771	1·557
Basic residue (g.)	0·145	0·129
Non-basic residue (g.)	0·968	0·916
N in non-basic residue (%)	0·82	0·76
Phenylpyridines (corr.) (g.)	0·789	0·694
Neutral diaryl fraction (corr.) (g.)	2·372	2·133
$Ph{\cdot}C_6H_4{\cdot}C_2H_5$ in neutral fraction (g.)	1·068	0·960
$Ph{\cdot}CO_2H$ (g.)	2·85	2·75
Benzoyl peroxide accounted for (%)	94·5	88
$^{PhEt}_{PyH}K$	1·16	1·19

Hence $^{PhEt}_{PyH}K = 1{\cdot}175$

TABLE 12.

Experiment:	14	15
Phenylpyridines (g.)	0·595	0·620
Neutral diaryl fraction (g.)	1·657	1·604
Basic residue (g.)	0·162	0·167
Non-basic residue (g.)	0·667	0·576
N in non-basic residue (%)	0·97	0·51
Phenylpyridines (corr.) (g.)	0·776	0·765
Neutral diaryl fraction (corr.) (g.)	2·078	1·999
$Ph{\cdot}C_6H_4{\cdot}Pr^i$ in neutral fraction (g.)	0·821	0·790
$Ph{\cdot}CO_2H$ (g.)	2·9	2·8
Benzoyl peroxide accounted for (%)	89	85
$^{PhisoPr}_{PyH}K$	0·84	0·82

Hence $^{PhisoPr}_{PyH}K = 0{\cdot}83$

The weights of ethyl- and *iso*propyl-diphenyls formed were obtained from the total weights of hydrocarbon by correcting for side-chain attack, using the data given in Tables 4 and 8.

By-products in the Phenylation of Toluene.—Benzoyl peroxide (50 g.) was allowed to decompose in toluene (500 ml.) in a thermostat at 80° for 72 hr. and the diaryl fraction of the product isolated by the standard procedure. The diaryl fraction was treated with an equal volume of light petroleum (b. p. 40—60°) and cooled to −80°. The solid which separated was removed by filtration and washed with cooled light petroleum. The solid (1·25 g.) was identified as dibenzyl (m. p. and mixed m. p. 51°). This comprised 13% of the weight of the diaryl fraction. Since, in the determination of the ratio of isomerides reported in Part VIII[15] the amount of 2-methyldiphenyl in the diaryl fraction was obtained by difference, this figure should be corrected for the dibenzyl formed as indicated above. The corrected values show 13% of side-chain attack and 87% of nuclear attack, and the product of nuclear attack contains 66·5% of 2-, 19·2% of 3-, and 14·3% of 4-methyldiphenyl. The altered ratio of isomerides leads to a change in the relative rate of phenylation and of the partial rate factor for the *ortho*-position, although those for the *meta*- and the *para*-position remain unaltered. The corrected partial rate factors are: F_o, 3·5;

F_m, 1·0; and F_p, 1·4. The general conclusions drawn concerning these partial rate factors are unaltered by this amendment.

Consideration of the spectroscopic evidence reported in Part VIII [15] for the presence of diphenylmethane in the product of this reaction led to attempts to isolate diphenylmethane from the diaryl fraction of the product of the reaction described above, and also from mixtures made up to contain 2-, 3-, and 4-methyldiphenyl and diphenylmethane. Physical methods, such as distillation, chromatography, and fractional freezing failed to effect the desired separation of the synthetic mixtures. Oxidation with chromic acid, followed by attempted isolation of benzophenone as its 2 : 4-dinitrophenylhydrazone, also proved unsatisfactory. The only method which could be used successfully with the synthetic mixtures was that employed by Yost and Hauser,[17] which involves the metallation of diphenylmethane with potassamide and treatment of the resulting diphenylmethylpotassium with solid carbon dioxide. Diphenylacetic acid was precipitated by addition of hydrochloric acid, and crystallised from light petroleum. From a synthetic mixture containing 20% of diphenylmethane, 15% was recovered as diphenylacetic acid in this way. A sample of the diaryl fraction of the product of the reaction of benzoyl peroxide with toluene, however, gave no diphenylacetic acid when subjected to this procedure, and it therefore seems that the presence of diphenylmethane in it is unlikely. The infrared absorption at 13·5 mμ which was assigned to diphenylmethane is therefore probably due to the presence of a little diphenyl, which absorbs at 13·49 mμ in nitromethane solution. Diphenyl was previously reported by De Tar [18] and by Hey, Nechvatal, and Robinson [19] to be formed in the reaction of benzoyl peroxide with nitrobenzene at high concentrations of the peroxide. It therefore seems not unlikely that diphenyl is also formed from high concentrations of benzoyl peroxide in toluene. The spectrum of a synthetic mixture containing 2-, 3-, and 4-methyldiphenyl together with about 5% of diphenyl, showed that the observed absorption could be accounted for by the presence of about this amount of diphenyl. However, all attempts to isolate diphenyl from the reaction product have failed. If the observed absorption at 13·5 mμ is in fact due to diphenyl, the dependence of its formation on the concentration of benzoyl peroxide is easily understood, since there is clearly a greater probability of the collision of two phenyl radicals under conditions of high concentration, especially since the present solvent, toluene, is relatively unreactive towards phenyl radicals.

Discussion

Reactivity of the Side-chain.—The proportions of side-chain and nuclear attack by phenyl radicals in the four alkylbenzenes so far investigated are as follows :

	Product of side-chain attack (% by wt.)	Product of nuclear attack (% by wt.)
Toluene	13	87
Ethylbenzene	55	45
*iso*Propylbenzene	60·5	39·5
tert.-Butylbenzene	0	100

The absence of attack on the side-chain of *tert.*-butylbenzene indicates that the reactivity of the β-hydrogen atoms of the side-chain is very low. This is not unexpected, since the radicals to which reactions of this type should give rise enjoy no stabilisation by resonance, and their stability, compared with that of the radicals resulting from attack in the α-position, must be very low. The reactivity of the α-hydrogen atoms is, however, seen to increase with increasing methylation of the α-position, notwithstanding their decreased number which results from successive replacement of them by methyl groups. This, again, must be due to the enhanced stability conferred on the radicals resulting from abstraction of hydrogen from the α-positions by the presence of adjacent methyl groups. This enhanced stability may arise from the hyperconjugation of the methyl groups.

The experiments described above also throw some light on the mechanism of the reaction of hydrogen-abstraction. Consideration of the results makes it possible to identify the attacking radical which is responsible for the abstraction of hydrogen as the phenyl radical and not the benzoyloxy-radical, since, with both ethylbenzene and *iso*propylbenzene, the amount of benzoic acid formed is grossly insufficient to account for the number of

[17] Yost and Hauser, *J. Amer. Chem. Soc.*, 1947, **69**, 2325.
[18] DeTar, *ibid.*, 1950, **72**, 1028.
[19] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.

benzoyloxy-radicals which must react in this way to give the observed amounts of the products derived from side-chain attack. On the other hand, benzene, resulting from hydrogen-abstraction by phenyl radicals, has been shown to occur in the products of reactions with ethylbenzene and *iso*propylbenzene. The work herein described shows that with benzoyl peroxide 60·5% of the product from *iso*propylbenzene consists of 2 : 3-dimethyl-2 : 3-diphenylbutane, while the remainder consists of products arising from nuclear substitution. Neither in this reaction nor in the preceding reaction with ethylbenzene could any evidence be obtained of substitution in the side-chain.

The results now reported are in complete agreement with a number of observations reported from other laboratories. For example, in 1939 Cuthbertson, Gee, and Rideal [20] discovered that the use of toluene as a solvent reduced the rate constant and degree of polymerisation of vinyl acetate, and they deduced that toluene was participating in the transfer mechanism. Other workers [21, 22] have shown that little or no retardation occurs with compounds which do not contain α-methylenic hydrogen atoms, and thus it appears that polymer radicals derived from the vinyl acetate must attack the methyl group of toluene. Jaquiss and Szwarc [23] studied the pyrolysis of benzyl benzoate in the presence of toluene at 700° and inferred that the following reactions must occur:

$$Ph{\cdot}CO{\cdot}O{\cdot}CH_2Ph \longrightarrow Ph{\cdot}CO{\cdot}O^{\cdot} + Ph{\cdot}CH_2^{\cdot} \quad (1)$$

$$Ph{\cdot}CO{\cdot}O^{\cdot} \longrightarrow Ph^{\cdot} + CO_2 \quad (2)$$

$$Ph{\cdot}CH_3 + Ph^{\cdot} \longrightarrow Ph{\cdot}CH_2^{\cdot} + PhH \quad (3)$$

$$2Ph{\cdot}CH_2^{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2Ph \quad (4)$$

They obtained a yield of dibenzyl greater than could be explained by reaction (1) alone, and thus postulated the occurrence of reaction (3). More recently McBay, Tucker, and Milligan [24] have allowed acetyl peroxide and several dialkyl peroxydicarbonates to undergo decomposition in toluene, and claim that a quantitative yield of dibenzyl is obtained when the ratio of toluene to radical source is large.

Kharasch, McBay, and Urry [3] have shown that methyl radicals derived from acetyl peroxide readily attack the alkyl group of ethylbenzene, abstracting hydrogen and yielding *meso*- and racemic 2 : 3-diphenylbutane in approximately equal quantities. Dannley and Zaremsky [16] have recently reported that the decomposition of benzoyl peroxide in ethylbenzene gave a product of which 65% by weight consisted of *meso*- and racemic 2 : 3-diphenylbutane, while the remainder was a mixture of the three isomeric ethyldiphenyls. With *iso*propylbenzene Kharasch, McBay, and Urry [3] claimed an almost quantitative yield of 2 : 3-dimethyl-2 : 3-diphenylbutane in the reaction with acetyl peroxide. In the decomposition of benzoyl peroxide in *iso*propylbenzene, Dannley and Zaremsky [16] reported that the product contained 31% of 2 : 3-dimethyl-2 : 3-diphenylbutane, whilst Rondestvedt and Blanchard [5] reported a yield of 59% of this hydrocarbon. Dannley and Zaremsky's figure would appear to be low, since it is clearly out of accord with the results of other workers (cf. Table 13). In addition, Rondesvedt and Blanchard obtained a similar ratio of nuclear to side-chain attack when they employed *N*-nitrosoacetanilide and 3 : 3-dimethyl-1-phenyltriazen as sources of phenyl radicals. This further supports the view that phenyl radicals alone abstract hydrogen from the side-chain of the alkylbenzene when benzoyl peroxide is used as the source of radicals.

Gregg and Mayo [21] have studied the inhibition of the polymerisation of styrene by various alkylbenzenes and noted that molecules containing α-hydrogen atoms appreciably reduced the molecular weight of the polymer. They suggested that such molecules transferred hydrogen atoms to the growing polymer radical, giving a substituted benzyl radical which did not participate further in the chain process. The transfer constants C for this process, which are proportional to the relative reactivities of the inhibitors, were measured and their values at 60° are shown in Table 13.

[20] Cuthbertson, Gee, and Rideal, *Proc. Roy. Soc.*, 1939, *A*, **170**, 300.
[21] Gregg and Mayo, *Discuss. Faraday Soc.*, 1947, **2**, 328.
[22] Kooyman, *ibid.*, 1951, **10**, 163.
[23] Jaquiss and Szwarc, *Nature*, 1952, **170**, 312.
[24] McBay, Tucker, and Milligan, *J. Org. Chem.*, 1954, **19**, 1003.

TABLE 13.

Compound	$C \times 10^5$ *	$K_r \times 10^3$ †	% Side-chain attack by Ph
Benzene	0·18	0·03	—
tert.-Butylbenzene	0·6	0·1	0
Toluene	1·25	0·42	13
Ethylbenzene	6·7	1·28	55
*iso*Propylbenzene	8·2	1·75	60·5

* Gregg and Mayo.[21] † Kooyman.[22]

Kooyman [23] has examined the reactivity of alkylbenzenes towards trichloromethyl radicals by a similar method. He measured the efficiency of various hydrocarbons as retarders in the free-radical addition of carbon tetrachloride to cet-1-ene. The values for various retarders of the quantity K_r, which is proportional to the reactivity of the retarder, are also shown in Table 13. The general agreement between the three sets of figures recorded in Table 13, which arise out of three separate and independent investigations directed towards entirely different objectives, is very satisfactory.

Russell and Brown[25] have recently measured the relative reactivity of the side-chains of toluene, *iso*propylbenzene, and *tert.*-butylbenzene towards photochemical chlorination, and have pointed out the close analogy between their results and those of Gregg and Mayo,[21] and of Kooyman.[22]

Ratios of Isomerides.—In Table 14 the relative amounts of the 2-, 3-, and 4-isomerides resulting from the phenylation of toluene, ethylbenzene, *iso*propylbenzene, and *tert.*-butylbenzene are compared with the relative amounts of the *ortho*-, *meta*-, and *para*-isomerides resulting from the nitration of these hydrocarbons (cf. Ingold [26]). The isomer ratios for the nitration of *iso*propylbenzene were measured by Brown and Bonner,[27] and those for the phenylation of *tert.*-butylbenzene by Cadogan, Hey, and Williams.[1a]

TABLE 14.

		PhMe	PhEt	PhPr^i	PhBu^t
Nitration	*ortho* (%)	57	55	30	11·8
	meta (%)	3	0	7·7	8·7
	para (%)	40	45	62·3	79·5
Phenylation	2- (%)	66·5	53	31	24
	3- (%)	19·2	28	42	49
	4- (%)	14·3	19	27	27

It is of interest that in both reactions the characteristic patterns of electrophilic and homolytic substitution, respectively, are shown by toluene and ethylbenzene, while in both reactions the proportion of the *ortho*(2)-isomer is drastically reduced when substitution is effected in the nuclei of *iso*propylbenzene and *tert.*-butylbenzene. This reduction has been attributed to the steric effect of the *iso*propyl and *tert.*-butyl groups, which inhibits substitution at the adjacent positions (Ingold; [26] Cadogan, Hey, and Williams [1a]).

Partial Rate Factors.—The rate of nuclear phenylation of ethylbenzene, relative to that of benzene as unity, is given by ${}^{PhEt}_{PhNO_2}K \times {}^{PhNO_2}_{PhH}K$, *i.e.*, $0{\cdot}31 \times 4{\cdot}0$ (cf. Part II [6]) $= 1{\cdot}24$. In the same manner, the rate of nuclear phenylation of *iso*propylbenzene, relative to that of benzene as unity, is calculated to be 0·87. The competitive experiments with mixtures of pyridine with ethylbenzene and with *iso*propylbenzene lead to values of ${}^{PhEt}_{PhH}K$ and ${}^{PhisoPr}_{PhH}K$ of 1·22 and 0·86 respectively [*e.g.*, ${}^{PhEt}_{PhH}K = {}^{PhEt}_{PyH}K \times {}^{PyH}_{PhH}K = 1{\cdot}175 \times 1{\cdot}04$ (cf. Part II [6])], thus confirming the values obtained by means of competitive experiments with nitrobenzene. These relative rates indicate that the behaviour of ethylbenzene is akin to that of toluene, the overall effect being one of mild activation. *iso*Propylbenzene, on the other hand, behaves like *tert.*-butylbenzene, the steric effect producing an overall deactivation of the nucleus. Partial rate factors for the phenylation of ethylbenzene and *iso*propylbenzene are calculated from the relative rates together with the mean values

[25] Russell and Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 4578.
[26] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, p. 258.
[27] Brown and Bonner, *J. Amer. Chem. Soc.*, 1954, **76**, 605.

obtained by spectrographic analysis for the ratio of isomerides resulting from nuclear phenylation. These factors, together with those obtained for toluene and *tert.*-butylbenzene (Part VII [16]) are given in Table 15.

TABLE 15. *Partial rate factors for phenylation.*

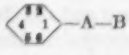
	F_o	F_m	F_p
Toluene	3·5	1·0	1·4
Ethylbenzene	1·97	1·04	1·41
*iso*Propylbenzene	0·81	1·1	1·41
tert.-Butylbenzene	0·63	1·28	1·41

The effects of the various alkyl groups on nuclear homolytic substitution are best assessed by consideration of the values of F_p, since these must be free from any complication arising from steric effects. This leads to the conclusion that, steric effects excepted, all of the alkyl groups influence the course of substitution in the same way and to the same extent, and that the degree of activation occasioned by them is, to a first approximation, independent of the alkyl group. The theoretical implication of this result is either (*a*) that the β-methyl groups are too remote from the aromatic nucleus for their influence to be significant, especially since no conjugation exists between them and the nucleus, or (*b*) that they exert a slight activating effect which is exactly compensated by the removal of the α-hydrogen atoms which their presence necessarily entails. These α-hydrogen atoms influence the nucleus by hyperconjugation, and their removal therefore results in some loss of activation. It is not easy to make a decision between these two possibilities, but on balance (*b*) seems the more likely explanation, partly on account of the inherent improbability of the complete lack of any effect required by (*a*), and partly because the activation of toluene relative to benzene suggests that the hyperconjugation of the α-hydrogen atoms in toluene is a real phenomenon.

Calculations by Wheland [28] of atom localisation energies for substitution in toluene are available for comparison with these experiments. Wheland calculated them for free-radical substitution in toluene and, by substitution of these in the Arrhenius equation, the following partial rate factors are obtained :

$$F_o = 1{\cdot}48 \qquad F_m = 0{\cdot}93 \qquad F_p = 1{\cdot}51$$

The agreement with experiment is good, especially since the predicted values depend exponentially on a small energy difference. Although no atom localisation energies have been derived for the remaining members of the series of alkylbenzenes, certain predictions can be made by consideration of the electronegativities of the alkyl substituents. Wheland considered the generalised structure :



and took into account only the π-electrons. In the secular equations the electronegativities of the various atoms were represented by dimensionless parameters δ_B, δ_A, δ_1, δ_2 - - - -. For toluene, if δ_A, δ_1, and δ_2 are put equal to −0·3, −0·1, and −0·01 respectively, and all the other quantities δ are considered to be zero, the equations give rise to atom localisation energies which give the above values for the partial rate factors for homolytic substitution and also give reasonable values for the partial rate factors for electrophilic substitution. Passing along the series of alkylbenzenes, there is a considerable change in the electronegativities of the substituents, and this gives rise to considerably altered partial rate factors for heterolytic substitution. In order to take account of this change the values −2·0 and −0·5 were used for the parameters δ_A and δ_1 in Wheland's equations for toluene. The increased steric effect was accommodated by the introduction of an increment of energy E_0(= 0·02 kcal. mole^{-1}) which was added to the atom localisation energy for the *ortho*-position. The values were chosen so as to give a reasonable approximation to the experimental partial rate factors for the nitration of *iso*propylbenzene. When they were used in Wheland's equations for homolytic substitution the following partial rate factors were

[28] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.

derived which correspond closely with the experimentally determined figures for *iso*-propylbenzene :

$$F_o = 0{\cdot}49 \qquad F_m = 0{\cdot}9 \qquad F_p = 1{\cdot}51$$

These values are in accord with the experimental result that free-radical substitution in the *meta*- and the *para*-position of alkylbenzenes is largely independent of the nature of the alkyl group.

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297. *Homolytic Aromatic Substitution. Part XII.* Reactions with Phenyl Iodosobenzoate.*

By D. H. HEY, C. J. M. STIRLING, and GARETH H. WILLIAMS.

The decomposition of phenyl iodosobenzoate in nitrobenzene at 125° has been shown to result in the formation of a mixture of isomeric nitrodiphenyls. The proportion in which these isomers occur in the mixture has been shown to be the same as that arising from the decomposition of benzoyl peroxide in the same solvent at the same temperature. This fact, coupled with the occurrence of by-products of the type usually associated with reactions of homolytic arylation, leads to the conclusion that benzoyloxy-radicals are produced by the homolytic decomposition of phenyl iodosobenzoate, and that phenyl radicals result from the benzoyloxy-radicals by loss of carbon dioxide. The anomalously high yield of benzoic acid which accompanies the reaction of phenyl iodosobenzoate with nitrobenzene has been shown most probably to arise from the hydrolysis of phenyl iodosobenzoate by the small amount of water present in the solvent. Phenyl iodosobenzoate has also been shown to be capable of effecting the carbon–carbon fission of the vicinal glycol, benzpinacol, by means of a non-homolytic mechanism.

CRIEGEE and BEUKER [1] have found that compounds of the type $RI(O{\cdot}CO{\cdot}R')_2$ (where R = aryl, R′ = alkyl) resemble lead tetra-acetate in their general reactions. In particular, they react with olefins to form glycol diacetates, and effect the fission of vicinal glycols. Sandin and McCormack [2] subsequently reported that *sym.*-trinitrotoluene was converted into *sym.*-trinitro-*m*-xylene in 20% yield by phenyl iodosoacetate in hot acetic acid. These authors recognised the analogy with the methylation of aromatic compounds with lead tetra-acetate,[3] and suggested that phenyl iodosoacetate might undergo homolytic decomposition to give methyl radicals in a manner analogous to that of lead tetra-acetate. Recently, in Parts VI [4] and X,[5] the reactions of lead tetrabenzoate have been investigated, and it was shown that homolytic decomposition takes place in inert aromatic solvents at temperatures above 100° with the production of free phenyl radicals. In addition, the reaction of lead tetrabenzoate with vicinal glycols at 15° was shown to result in fission, and so to be quite distinct from the high-temperature decomposition and not to involve free radicals. No work appears to have been carried out on phenyl iodosobenzoate as a potential phenylating agent. In the present communication the reactions of phenyl iodosobenzoate have been investigated with reference to the known reactions of benzoyl peroxide and lead tetrabenzoate.

* Part XI, preceding paper.

[1] Criegee and Beuker, *Annalen*, 1939, **541**, 218.
[2] Sandin and McCormack, *J. Amer. Chem. Soc.*, 1945, **67**, 2051.
[3] Fieser, Clapp, and Daudt, *ibid.*, 1942, **64**, 2052.
[4] Hey, Stirling, and Williams, *J.*, 1954, 2747.
[5] *Idem*, *J.*, 1955, 3963.

Phenyl iodosobenzoate was first prepared by Arbuzov.[6] In 1949, Richards [7] described the use of phenyl iodosobenzoate and other phenyl iodosoacylates as catalysts in addition polymerisation. It is now shown that the decomposition of phenyl iodosobenzoate in nitrobenzene gives rise to nuclear phenylation, a mixture of the three isomeric nitrodiphenyls being obtained. The composition of the mixture has been determined by ultraviolet spectroscopy and the results are in very close agreement with those obtained in similar reactions with benzoyl peroxide and lead tetrabenzoate.[4] The phenylation of pyridine with phenyl iodosobenzoate has been reported in Part X.[5] Thus it is clear that the phenylating action of phenyl iodosobenzoate is closely analogous to that of benzoyl peroxide, lead tetrabenzoate, and the various diazo-derivatives discussed in Part I by Hey, Nechvatal, and Robinson.[8] At temperatures above 100°, phenyl iodosobenzoate undergoes homolytic decomposition to liberate benzoyloxy-radicals which, by subsequent decarboxylation, provide phenyl radicals.

The decomposition of phenyl iodosobenzoate has been shown to afford an anomalously high yield of benzoic acid (1·43 mol./mol.) in nitrobenzene. Free benzoic acid can arise in the decomposition in only two ways : (1) By combination of a benzoyloxy-radical with a free hydrogen atom which has been liberated from the nitrobenzene nucleus during substitution by a benzoyloxy or phenyl radical :

$$\mathrm{Ph\cdot \text{ or } Ph{\cdot}CO{\cdot}O{\cdot} + ArH \longrightarrow Ph{\cdot}Ar \text{ or } Ph{\cdot}CO_2Ar + H\cdot}$$
$$\mathrm{H\cdot + Ph{\cdot}CO{\cdot}O{\cdot} \longrightarrow Ph{\cdot}CO_2H}$$

(2) By the attack of a free hydrogen atom on phenyl iodosobenzoate :

$$\mathrm{PhI(O{\cdot}CO{\cdot}Ph)_2 + H\cdot \longrightarrow PhI + Ph{\cdot}CO{\cdot}O{\cdot} + Ph{\cdot}CO_2H}$$

Mechanisms involving the abstraction by benzoyloxy-radicals of nuclear hydrogen atoms from the aromatic solvent are not tenable, since in the case of nitrobenzene, for example, the process must yield an amount of dinitrodiphenyl equivalent to the benzoic acid formed by this mechanism :

$$\mathrm{Ph{\cdot}CO{\cdot}O{\cdot} + Ar{\cdot}H \longrightarrow Ph{\cdot}CO_2H + Ar\cdot}$$
$$\mathrm{Ar\cdot + Ar{\cdot}H \longrightarrow Ar{\cdot}Ar + H\cdot}$$

No products corresponding to Ar·Ar were formed in any of the reactions studied.

As the free benzoic acid can therefore arise only by mechanisms (1) and (2), its molar yield should ideally be equal to the sum of the molar yields of diaryl and " ester " benzoic acid, which is obtained by hydrolysis of the products of substitution by benzoyloxy-radicals and, in any case, should not be greater than unity. In the decomposition of phenyl iodosobenzoate, however, the molar yield of free benzoic acid is 1·43, while the sum of the molar yields of nitrodiphenyl and " ester " acid is 0·50. The following possible sources of benzoic acid in the decomposition and subsequent working-up have therefore been checked and a probable explanation of the anomaly has been found.

(*a*) Incomplete decomposition of the reagent with subsequent hydrolysis of undecomposed starting material : The fact that decomposition was complete was readily established by testing for phenyl iodosobenzoate with starch–iodide. Negative results were obtained in every case and, moreover, an increase in the period of heating did not affect the yield of free benzoic acid.

(*b*) Formation of benzoic anhydride : Lippmann [9] has implied that benzoic anhydride is formed in the decomposition of benzoyl peroxide in " amylene." In order to account on an analogous basis for the yield of benzoic acid formed in the present reactions, any benzoic anhydride produced in the decomposition of phenyl iodosobenzoate must be hydrolysed during the extraction of the free acid. It has, however, been shown that benzoic

[6] Arbuzov, *J. prakt. Chem.*, 1931, **131**, 357.
[7] Richards, U.S.P. 2,467,231.
[8] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.
[9] Lippmann, *Monatsh.*, 1884, **5**, 559.

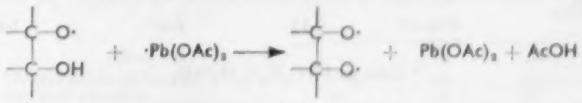
anhydride is not appreciably hydrolysed by saturated aqueous sodium hydrogen carbonate under the conditions used in the working up.

(*c*) Hydrolysis of esters: It was shown that no benzoic acid was formed when a mixture of phenyl benzoate with the three isomeric nitrophenyl benzoates was treated with aqueous sodium hydrogen carbonate under the conditions used for the extraction of the free acid.

(*d*) Presence of water in the solvent: Determination of the concentration of water in the nitrobenzene showed that the amount present is just sufficient to account for the amount of benzoic acid obtained. Addition of excess of water to the reaction mixture has been shown (Table 1) to result in a substantial increase in the yield of benzoic acid, with a corresponding decrease in the yields of the products of nuclear phenylation and benzoyloxylation, although even in the presence of a considerable excess of water the hydrolysis is not quite quantitative. Thus the rate of the homolysis must be sufficiently large compared with the rate of hydrolysis, so that the former reaction still takes place to a minor extent. It would appear, therefore, that hydrolysis of phenyl iodosobenzoate by the small amount of water present in the solvent provides the most likely explanation of the high yield of benzoic acid, although this does not necessarily exclude the possibility that other factors may contribute.

In addition to the investigation of the homolytic decomposition of phenyl iodosobenzoate it has now been shown that this reagent is capable of effecting carbon–carbon fission in a vicinal glycol by a non-homolytic process. Phenyl iodosobenzoate reacts rapidly with benzpinacol in benzene solution at 80° to give a quantitative yield of benzophenone, with the consumption of an equivalent amount of phenyl iodosobenzoate. No products corresponding to a free-radical reaction could be found.[10] The correspondence between the reactions of lead tetrabenzoate and those of phenyl iodosobenzoate is thus established.

A comparison of the reactions of lead tetra-acetate and of acetyl peroxide has been reported by Kharasch, Friedlander, and Urry.[11] Whereas the reaction of a vicinal glycol with lead tetra-acetate results in cleavage of a carbon–carbon bond, that with acetyl peroxide results in oxidation to a hydroxy-ketone and finally a diketone. The reaction which results in the fission of vicinal glycols does not possess any of the characteristics of a homolytic process. This same contrast has been shown between the reactions of a vicinal glycol with lead tetrabenzoate on the one hand and benzoyl peroxide on the other (cf. Part VI [4]). The reactions of phenyl iodosobenzoate clearly follow very closely the pattern shown by lead tetrabenzoate, and both reagents effect the fission of vicinal glycols at temperatures well below those at which homolytic decomposition occurs. The conclusions thus reached are at variance with those put forward by Cordner and Pausacker [12] for the oxidation of vicinal glycols with lead tetra-acetate and phenyl iodosoacetate. These authors postulate the intermediate formation of a triacetoxylead radical, which reacts *specifically* upon the hydrogen atom of the adjacent hydroxyl group, thus:



Free radicals are, in general, notably non-selective in their reactions and it seems unlikely that a triacetoxylead radical would take part in such a highly specific reaction to the extent required for the almost quantitative character of the reaction. Such triacetoxylead radicals have been postulated by Kharasch and his co-workers [11] in the high-temperature decomposition of lead tetra-acetate and are considered to break down further into lead acetate and acetoxyl radicals. Moreover, the present demonstration that lead tetrabenzoate and phenyl iodosobenzoate react with vicinal gycols by a non-homolytic mechanism renders unlikely the intervention of free radicals in the analogous reactions with lead tetra-acetate and phenyl iodosoacetate.

[10] Cf. ref. 4.
[11] Kharasch, Friedlander, and Urry, *J. Org. Chem.*, 1949, **14**, 91; 1951, **16**, 533.
[12] Cordner and Pausacker, *J.*, 1953, 102; Pausacker, *ibid.*, p. 107.

Experimental

Reagents.—Nitrobenzene ("AnalaR") was purified as previously described.[4] The water content of nitrobenzene purified in this way, as determined by the Karl Fischer method, was 0·1% w/v. Chloroform was dried and freed from ethanol with calcium chloride. Benzoic anhydride (Hopkin and Williams) was crystallised to constant m. p. 41°. Benzpinacol was prepared by the reduction of benzophenone with zinc and acetic acid.[13] It crystallised from benzene–light petroleum (b. p. 40—60°) in white needles, m. p. 186—187°.

Phenyl iodosobenzoate was prepared by a modification of Arbuzov's method.[6] Iodosobenzene[14] (37 g.) was added to a solution of benzoic acid (41 g.) in chloroform (500 ml.). The mixture was shaken gently until the iodosobenzene had dissolved, and the solution was then filtered. Chloroform was distilled off from the filtrate, and the solid residue was thoroughly washed with boiling light petroleum (b. p. 40—60°) (2 × 100 ml.). The crude material was recrystallised from chloroform–light petroleum, to yield phenyl iodosobenzoate, m. p. 159—160° (62 g.) (Found: C, 53·8; H, 3·3%; equiv., 223. Calc. for $C_{20}H_{15}O_4I$: C, 53·8; H, 3·4%; equiv., 223). The equivalent was determined iodometrically by the method used for lead tetrabenzoate.[4]

Decomposition of Phenyl Iodosobenzoate in Nitrobenzene.—Reactions were carried out in duplicate in a thermostat maintained at 125° ± 0·1° by the method previously used by Augood, Hey, and Williams in Part II.[15] Reaction flasks containing nitrobenzene (190 ml.) were placed in the thermostat 1 hr. before addition of the reagent. Phenyl iodosobenzoate (11·15 g.) was slowly added to the nitrobenzene with shaking, and a further 10 ml. of solvent were added dropwise. The mixtures were removed from the thermostat after 72 hr., reactions then being complete. The cold mixtures were extracted with saturated sodium hydrogen carbonate solution (3 × 75 ml.), and washed with water. Nitrobenzene was removed by distillation at 20 mm. through a 25 cm. helix-packed column. Esters in the residue were hydrolysed by boiling with 150 ml. of 2N-sodium hydroxide for 15 hr. The unsaponifiable material was thoroughly extracted with benzene (3 × 50 ml.), and the benzene extracts, after being dried ($CaCl_2$), together with benzene washings of the calcium chloride, were reduced in volume by distillation to 70 ml. The residue from the distillation was chromatographed on an alumina column (25 × 2 cm.) and eluted successively with benzene (100 ml.) and with ether (100 ml.). Ether and benzene were removed from the combined eluates by distillation through a 25 cm. helix-packed column, and subsequent distillation of the residue by the method described by Augood, Hey, and Williams[15] gave a mixture of nitrodiphenyls as a pale yellow semi-solid b. p. 118—138°/0·5 mm. The products obtained from these reactions are listed in Table 1. Expt. 3 was carried out under the

Table 1. *Products obtained in reactions with nitrobenzene at* 125° *(mol./mol. of reagent).*

Reagent	Free $Ph{\cdot}CO_2H$	$Ph{\cdot}CO_2H$ from ester	$Ph{\cdot}C_6H_4{\cdot}NO_2$	Higher phenylated products *
$PhI(O{\cdot}CO{\cdot}Ph)_2$				
1 & 2 (mean)	1·43	0·27	0·23	0·01
3	1·84	0·02	0·10	0·01
4	1·43	—	—	—
$(Ph{\cdot}CO_2)_2$				
5	0·74	0·11	0·65	0·03
6	0·75	—	—	—

* Calc. as $Ph{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}NO_2$.

same conditions, except that water (1·80 g., 0·05 mol./mol. of nitrobenzene) was added to the nitrobenzene. Expt. 4 was carried out under the same conditions as expts. 1 and 2, except that the reagent was dissolved in cold nitrobenzene. The apparatus was closed with a phosphoric oxide tube in addition to the calcium chloride tube, and then placed in the thermostat. The period of heating was extended to 96 hr. in this experiment. The results of expt. 5 are quoted in Part VI,[4] and expt. 6 was carried out under the same conditions as expt. 5 with the addition of water (0·9 g.). Analyses for nitrogen on the mixtures of isomeric nitrodiphenyls were as follows: (1) 7·25; (2) 6·85; (3) 6·95 (Calc. for $C_{12}H_9O_2N$: N, 7·0%). The phenyl iodosobenzoate accounted for as products derived from benzoyloxy-radicals in expts. 1 and 2 amounts to 95%.

[13] Sagumenny, *Bull. Soc. chim. France*, 1880, **34**, 329.
[14] Lucas, Kennedy and Formo, *Org. Synth.*, 1942, **22**, 70.
[15] Augood, Hey, and Williams, *J.*, 1952, 2094.

Free benzoic acid formed in these reactions was isolated as follows: the sodium hydrogen carbonate extracts of the reaction mixture were washed with methylene chloride, acidified with concentrated hydrochloric acid, and then saturated with sodium chloride. The precipitated benzoic acid was thoroughly extracted with methylene chloride (4 × 30 ml.). The aqueous layer was rejected and the combined extracts, after being dried (Na_2SO_4), were allowed to evaporate at room temperature. The residual benzoic acid had m. p. and mixed m. p. 117—119°. Benzoic acid which resulted from the hydrolysis of esters was isolated in the same manner as the benzoic acid formed in the phenylation of pyridine.[5]

Extent of Hydrolysis of Benzoic Anhydride.—Benzoic anhydride (3·0 g.) was dissolved in benzene (75 ml.). The solution was treated in the same manner as for the isolation of free benzoic acid. Benzoic acid (0·05 g.), m. p. and mixed m. p. 120°, was obtained.

Hydrolysis of Esters.—A mixture of equal quantities of phenyl benzoate with each of the isomeric nitrophenyl benzoates (2 g.) was dissolved in benzene (75 ml.), and the solution was treated in the same manner as in the experiment described above with benzoic anhydride. No benzoic acid was obtained.

Hydrolysis of Phenyl Iodosobenzoate by Water Present in the Solvent.—A Karl Fischer determination of the water present in the nitrobenzene showed the concentration to be $5·5 \times 10^{-3}$ mol./mol. The concentration of the reagent used was $12·5 \times 10^{-3}$ mol./mol. If each mole of water caused the hydrolysis of one mole of phenyl iodosobenzoate with the production of two moles of benzoic acid, and if hydrolysis were quantitative, the yield of free benzoic acid could be accounted for. Thus, in expts. 1 and 2 (Table 1), the excess of free benzoic acid over the sum of the yields of diaryls and " ester " benzoic acid is 0·93 mole/mole of reagent. This is the amount of benzoic acid which must be accounted for by hydrolysis of the reagent, if it is assumed that the extraction of nitrodiphenyls and " ester " benzoic acid is quantitative. The amount of water present in the nitrobenzene used (200 ml.) amounts to 0·20 g. on the basis of the Karl Fischer determinations. This is capable of producing 0·022 mole of benzoic acid by the hydrolysis of phenyl iodosobenzoate, and since 11·15 g. of phenyl iodosobenzoate were used, this represents a yield of 0·89 mole of benzoic acid per mole of phenyl iodosobenzoate. Thus the discrepancy in the yield of benzoic acid is reduced to 0·04 mole/mole of reagent, and since the extraction of nitrodiphenyl and " ester " benzoic acid is certainly not quantitative, and a 5% error in the Karl Fischer estimation perfectly conceivable, the result is probably well within the limits of accuracy of the experiment.

Determination of the Composition of the Mixture of Nitrodiphenyls.—The determination of the ratio of isomers present in the mixture of isomeric nitrodiphenyls formed in the decomposition of phenyl iodosobenzoate in nitrobenzene was carried out by ultraviolet spectrophotometry with the aid of a Unicam " S.P. 500 " quartz spectrophotometer, the method of calculation described by Cadogan, Hey, and Williams [16] being used. The calibration curves for the pure isomers had been obtained previously.[4] The compositions of the mixtures obtained by this means are given in Table 2. The overall error of each determination was ±2%. The results obtained in similar reactions with benzoyl peroxide, which are quoted from Part VI,[4] are included for comparison.

TABLE 2. *Mean isomer ratios in reactions with nitrobenzene at* 125°.

Reagent	Isomers (%)		
	o-	*m*-	*p*-
Phenyl iodosobenzoate	57·5	14	28·5
Benzoyl peroxide	56	16	28

Reaction of Phenyl Iodosobenzoate with Benzpinacol.—A mixture of benzpinacol (3·2280 g.) and phenyl iodosobenzoate (4·4809 g.) was dissolved in sodium-dried " AnalaR " benzene (100 ml.). The solution was boiled under reflux for 60 min. and then cooled rapidly to room temperature. 10% Sulphuric acid (50 ml.) and excess of potassium iodide were added, and the liberated iodine was titrated with 0·05N-sodium thiosulphate. The aqueous layer was made alkaline with sodium hydrogen carbonate and thoroughly extracted with benzene (2 × 35 ml.). Benzoic acid (m. p. and mixed m. p. 119°) was isolated from the aqueous solution in the manner described above. The benzene extracts, after being dried (Na_2SO_4), were reduced to a small volume by distillation through a 25 cm. helix-packed column. Distillation of the residue yielded first iodobenzene, b. p. 110°/50 mm. (converted to 1-iodo-4-nitrobenzene, m. p. and mixed m. p.

[16] Cadogan, Hey, and Williams, *J.*, 1954, 794.

171°), and subsequently benzophenone, b. p. 90°/0·2 mm., m. p. and mixed m. p. 46—47°. The results of experiments carried out in duplicate are shown in Table 3.

TABLE 3. *Results obtained in the oxidation of benzpinacol with phenyl iodosobenzoate.*

	Mol./mol. of benzpinacol	
	(1)	(2)
Yield of benzophenone	1·97	1·91
Phenyl iodosobenzoate consumed	1·00	1·00

Grateful acknowledgement is made to Messrs. May & Baker Ltd., Dagenham, for the Karl Fischer determinations of water in the samples of nitrobenzene, and to the Department of Scientific and Industrial Research for the award of a Maintenance Grant (to C. J. M. S.).

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298. *Some Chain-substituted Methincyanines and Styryl Dyes.*

By FRANCES M. HAMER.

Various methincyanines carrying a substituent on the chain have been prepared and their absorption maxima compared with those of the parent dyes. On substitution there are large bathochromic shifts for methyl, 2-benzothiazolyl, phenyl, and *p*-nitrophenyl; for carbethoxy, in the thiacyanine series, the shifts are also bathochromic but smaller, whilst in the thia-2′-cyanine series they are hypsochromic. Introduction of substituents into the α-position in the chain of styryl dyes causes hypsochromic shifts of the absorption maximum.

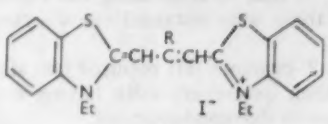
THE introduction of a substituent into the chain of a trimethincyanine has, until recently, been known to produce only slight colour changes. For example, passage from the benzothiazole dye (I; R = H) to its analogues (I; R = Me) and (I; R = Ph) caused the absorption maximum to undergo a hypsochromic shift of 145 Å, and a bathochromic shift of 25 Å, respectively.[1] Comparable with these are bathochromic shifts of 70—100 Å on passing from the same dye (I; R = H) to the analogue where R = NAcR′, whereas hypsochromic shifts of 620, 890, and 560—880 Å, respectively, on passing [2] to dyes where R = OMe, NEt_2, and NHR′ are of a different order.

In the methincyanine series, Götze [3] actually made the first chain-substituted member (II; R = Me, R′ = R″ = Et) but, because it gave a violet solution whereas the unsubstituted dye gave an orange one, he did not believe them to be so simply related;[3] the colour change produced by introduction of this methyl group in fact corresponds to a bathochromic shift of 590 Å. In another methincyanine series (III), it has been recorded [4] that replacement of :CH· by :CMe· caused a bathochromic shift of 605 Å. In another, (IV; R′ = R″ = Me), a bathochromic shift of 430 Å, or 445 Å, was recorded for this displacement.[5,6] A striking instance is replacement [7] of :CH· by :C(OH)· in this dye (IV; R′ = R″ = Me), where the bathochromic shift amounted to 750 Å, and treatment with triethylamine caused a further such shift of 1060 Å.

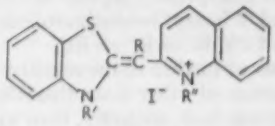
In contrast with the record of these large bathochromic shifts is the statement that no change of absorption maximum occurred on passing from a dye (IV; R = H, R′ = Me, R″ uncertain) to its ethoxycarbonyl derivative (IV; R = CO_2Et, R′ = Me, R″ uncertain).[8] Because of its anomalous character, this result is particularly important and it is a pity that preparative details and analyses were not published.

[1] Brooker and White, *J. Amer. Chem. Soc.*, 1935, **57**, 2480.
[2] Sveshnikov, Levkoev, Portnaya, and Lifshits, *Doklady Akad. Nauk S.S.S.R.*, 1952, **84**, 733.
[3] Götze, *Angew. Chem.*, 1936, **49**, 563.
[4] Brooker, White, Sprague, Dent, and van Zandt, *Chem. Rev.*, 1947, **41**, 325.
[5] Kiprianov and Ushenko, *J. Gen. Chem.* (*U.S.S.R.*), 1950, **20**, 139 (*Zhur. obshchei Khim.*, p. 134) (in this and a similar citation, the first refers to the U.S. translation, the second to the Russian original).
[6] Fry and Kendall, *J.*, 1951, 1723.
[7] Jeffreys, *J.*, 1954, 503.
[8] Van Dormael and Nys, 21st Congr. Chim. Ind., 1948, 483; *Chimie et Industrie*, 1950, **63**, 483.

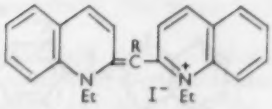
In a typical thia-2′-cyanine condensation, 2-methylbenzothiazole ethiodide was condensed with 2-iodoquinoline ethiodide to give the cyanine (II; R = H, R′ = R″ = Et);[9] by modifying the conditions, the yield was increased[10] to 88%. For *meso*-substituted dyes, benzothiazole ethiodides having a substituted 2-methyl group were



(I)



(II)



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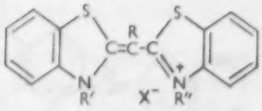


(IV)

required. When the ethiodide of pure 2-ethylbenzothiazole[11] was now condensed with 2-iodoquinoline ethiodide, the yield of *meso*-methyl dye (II; R = Me, R′ = R″ = Et) was 59% and it was unaccompanied by any dye by-product, although Götze[3] obtained one. However, when 2-ethylthioquinoline ethiodide was used instead of 2-iodoquinoline ethiodide, the yield of *meso*-methyl dye was greatly reduced and it was accompanied by the unsubstituted dye (II; R = H, R′ = R″ = Et). Similarly, reaction of 2-ethylthiobenzothiazole ethiodide with 2-ethylbenzothiazole ethiodide gave the required product (IV; R = Me, R′ = R″ = Et, X = I), accompanied by the unsubstituted dye (IV; R = H, R′ = R″ = Et, X = I). Fry and Kendall have recorded that the methyl analogue (IV; R = R′ = R″ = Me) is accompanied by its " parent " (IV; R = H, R′ = R″ = Me).[6]

By condensation of 2-benzylbenzothiazole ethiodide with 2-iodoquinoline ethiodide, the *meso*-phenyl dye (II; R = Ph, R′ = R″ = Et) was produced in 60% yield. 2-Ethyl- and 2-benzyl-benzothiazole ethiodide, respectively, with 2-iodo-5 : 6-benzoquinoline ethiodide, gave the more complex analogues (V; R = Me and Ph, R′ = R″ = Et), the yields being 67% and 42% as against 42% for the parent (V; R = H, R′ = R″ = Et). Similar condensations with 1-iodo*iso*quinoline ethiodide led to the *iso*quinoline dyes (VI; R = Me, R′ = R″ = Et, X = ClO_4) and (VI; R = Ph, R′ = R″ = Et, X = I), in 72% and 36% yield, respectively; the 41% yield for the parent (VI; R = H, R′ = R″ = Et, X = I), obtained[12] by use of sodium ethoxide, could probably be improved by use of triethylamine. The thia-2′-cyanine condensation has been successfully extended to the preparation of chain-substituted methincyanines, the yields being comparable with those of the unsubstituted parent dyes.

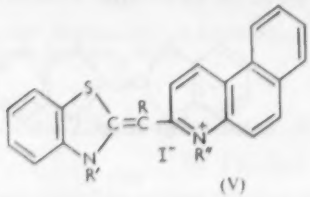
The thia-4′-cyanine condensation, on the other hand, could not be extended in a similar way. According to that, 2-methylbenzothiazole ethiodide was condensed with quinoline ethiodide to give the 4′-cyanine (VII; R = H, R′ = R″ = Et), acid and hydrogen being eliminated;[13] under improved conditions, the yield had been raised[14] to 63%. Use of 2-ethyl- in place of 2-methyl-benzothiazole ethiodide now gave a negative result so far as the dye (VII; R = Me, R′ = R″ = Et) was concerned; dyes were indeed produced in low yield, but they were identified as xantho- and erythro-*apo*cyanines, which are known to be formed by the action of alkali on quinoline ethiodide.[15,16] This negative result for

[9] Hamer, *J.*, 1928, 206.
[10] Brooker and Keyes, *J. Amer. Chem. Soc.*, 1935, **57**, 3488.
[11] Hamer, Rathbone, and Winton, *J.*, 1947, 954.
[12] Fisher and Hamer, *J.*, 1934, 1905.
[13] Braunholtz and Mills, *J.*, 1922, **121**, 2004.
[14] Keyes and Brooker, *J. Amer. Chem. Soc.*, 1937, **59**, 74.
[15] Kaufmann and Strübin, *Ber.*, 1911, **44**, 690.
[16] Mills and Ordish, *J.*, 1928, 81.

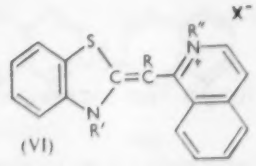
the *meso*-methylthia-4′-cyanine disagrees with a claim that 2-ethylbenzoselenazole ethiodide was condensed with *p*-toluquinoline ethiodide to give a *meso*-methylselena-4′-cyanine.[17]

Alternatively, thia-4′-cyanines had been synthesised by a modified thia-2′-cyanine condensation, in which 4-iodoquinoline ethiodide took the part of its 2-isomeride.[18] This reaction has now proved capable of extension, so that by condensing the 4-iodo-salt with 2-ethyl- and 2-benzyl-benzothiazolium salts, there were obtained the 4′-cyanines (VII; R = Me and Ph, R′ = R″ = Et).

Synthesis of further chain-substituted thia-2′-cyanines (II) required two stages: first, the preparation of other benzothiazoles and their quaternary salts, having a substituted 2-methyl group, and, secondly, their application in dye condensations.



(V)



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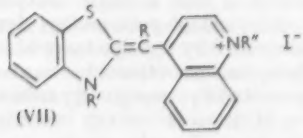
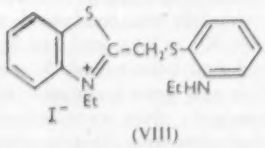


(VII)

Both steps were realised in the preparation of the ethiodide of a new base, 2-*p*-nitrobenzylbenzothiazole and, from it, of the dye (II; R = *p*-$C_6H_4 \cdot NO_2$, R′ = R″ = Et).

2-Chloromethylbenzothiazole is also described for the first time, but it could not be converted into a quaternary salt: this corresponds with a reported failure to prepare a quaternary salt of 2-bromomethylbenzothiazole.[19] However, Kiprianov and Pazenko's general method for preparing quaternary benzothiazolium salts, by the action of acid halides on *N*-substituted *o*-aminothiophenol [20] was applied by them to the preparation of 2-bromomethylbenzothiazole methobromide,[20] and it was hoped to apply it to the ethiodide of 2-chloromethylbenzothiazole. This hope was not realised, although Yagupolsky and Marenets had isolated 2-chloromethylbenzothiazole ethochloride: [21] reaction of *o*-ethylaminothiophenol with excess of chloroacetyl chloride, followed by potassium iodide, did give an ethiodide, but by analysis the product was identified as the sulphide (VIII). This resembles the product (IX) which Kiprianov and Pazenko obtained from *o*-methylaminothiophenol and dichloroacetyl chloride.[20]



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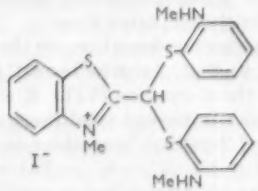


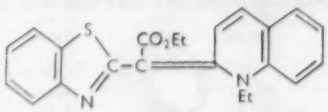
(IX)

2-Ethoxycarbonylmethylbenzothiazole was prepared by van Dormael and Nys, who used the crude base for dye condensations and made its methiodide.[22] The base has now

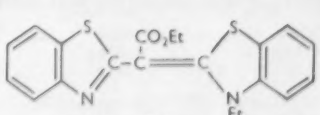
[17] Dieterle, Zeh, and Agfa Ansco Corp., U.S.P. 2,051,134/1931.
[18] Hamer, *J.*, 1939, 1008.
[19] Zubarovsky, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 2055.
[20] Kiprianov and Pazenko, *ibid.*, 1949, **19**, 1515.
[21] Yagupolsky and Marenets, *ibid.*, 1953, **23**, 497.
[22] Van Dormael and Nys, *Bull. Soc. chim. belges*, 1948, **57**, 355.

been distilled and obtained analytically pure. Their preparation of the methiodide by heating the base with methyl iodide in a sealed tube at 65° was confirmed, but at 100° the product was 2-methylbenzothiazole methiodide. When the base was heated with ethyl iodide in a sealed tube at 65°, salt formation did not occur, whilst at 100° the product was 2-methylbenzothiazole ethiodide, but 2-ethoxycarbonylmethylbenzothiazole ethiodide was arrived at by applying the general method of Kiprianov and Pazenko,[20] the reactants in this case being *o*-ethylaminothiophenol and ethoxycarbonylacetyl chloride. Unfortunately attempts to convert this ethiodide into methincyanines having a *meso*-ethoxycarbonyl group (II and IV; R = CO_2Et, R′ = R″ = Et) were unsuccessful. At first sight this is surprising, since it was noted long ago that quaternary salts undergo certain condensations more readily than do the corresponding bases,[23] and indeed the whole chemistry of cyanines may be regarded as based on that theorem. However, there are exceptions and it has recently been recorded [24] that 2-ethylpyridine, but not its methiodide, condensed with aldehydes.

As its ethiodide could not be used, 2-ethoxycarbonylmethylbenzothiazole was condensed with the ethosulphates of 2-ethylthioquinoline and 2-ethylthiobenzothiazole severally to give the dye bases (X) and (XI), the condensations being effected as indicated by van Dormael and Nys [8] for the *N*-methyl analogue of the latter. The bases were purified through their perchlorates. Attempts to use similarly 2-(ethoxycarbonylformyl)methylbenzothiazole,[25] in order to reach analogues of (X) and (XI) having a *meso*-ethoxalyl group,



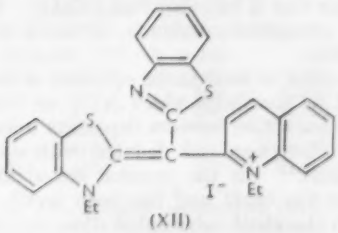
(X)



(XI)

led only to the corresponding unsubstituted bases; in an attempt to condense 2-chloromethylbenzothiazole with 2-ethylthioquinoline ethosulphate, dye formation did not take place. By the action of alkyl halides on the bases (X) and (XI), two pairs of chain-substituted methincyanines were prepared, *viz.*, (II; R = CO_2Et, R′ = Me or Et, R″ = Et) and (IV; R = CO_2Et, R′ = Me or Et, R″ = Et).

By reaction of di(benzothiazolyl)methane ethiodide [26] with 2-iodoquinoline ethiodide there was prepared the cyanine (XII), in which the *meso*-substituent is particularly large. Use of a quaternary salt of di(benzothiazolyl)methane in a cyanine-dye condensation has



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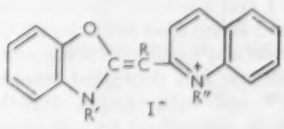


(XIII)

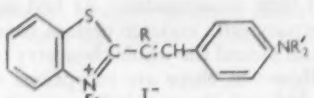
not previously been described, although the base itself was used for making trinuclear *mero*cyanines.[27]

Condensing quaternary salts of 2-ethyl- and 2-benzyl-benzoxazole with 2-iodoquinoline ethiodide gave the cyanines (XIII; R = Me or Ph, R′ = R″ = Et), which are the benzoxazole analogues of (II; R = Me or Ph, R′ = R″ = Et). The benzoxazole

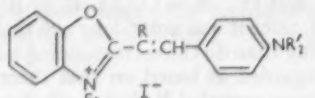
[23] Kaufmann and Vallette, *Ber.*, 1912, **45**, 1736.
[24] Phillips, *J. Amer. Chem. Soc.*, 1954, **76**, 3986.
[25] Borsche and Doeller, *Annalen*, 1939, **537**, 53.
[26] Mills, *J.*, 1922, **121**, 455.
[27] Anish and General Aniline and Film Corp., B.P. 620,482/1945.

analogues of (V and VII; R = Ph, R′ = R″ = Et) and that of (VI; R = Ph, R′ = R″ = Et, X = I) were also obtained. Owing to their instability, the benzoxazole analogues were more difficult to isolate than the benzothiazole dyes.

In the styryl series, the parent ethiodide (XIV; R′ = Me, R = H) is known.[28] Kiprianov and Ushenko [29] prepared the corresponding perchlorate and made an interesting study of chain-substituted styryl dyes, including the perchlorates corresponding with the iodides (XIV; R′ = Me, R = Me or Ph). Five chain-substituted styryl dyes have now been made, namely, (XIV; R′ = Me, R = Me, Ph, *p*-$C_6H_4{\cdot}NO_2$, CO_2Et, or 2-benzothi-



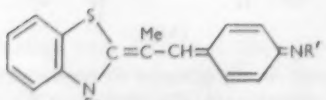
(XIV)



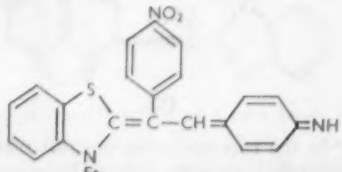
(XV)

azolyl). Another unsubstituted parent dye and its methyl derivative (XIV; R′ = Et, R = H and Me) were also made. In the benzoxazole series there were prepared the parent dye (XV; R′ = Me, R = H) and two derivatives (XV; R′ = Me, R = Me or Ph).

It was noticed that the dye (XIV; R′ = R = Me) was accompanied by a basic by-product. So also was the closely related product (XIV; R′ = Et, R = Me) whereas the unsubstituted parent (XIV; R′ = Et, R = H) was not. These by-products were purified and analysed; it was concluded that both *N*-methyl groups, but only one *N*-ethyl group,



(XVI)



(XVII)

was lost in formation of the by-products, which were the imines (XVI; R = H or Et). The latter by-product may be simply derived from (XIV; R′ = Et, R = Me) by elimination of ethyl iodide; to arrive at the former by-product from (XIV; R′ = R = Me), methyl iodide may be eliminated, hydrogen iodide added, and methyl iodide again eliminated. A basic by-product also accompanied the dye (XIV; R′ = Me, R = *p*-$C_6H_4{\cdot}NO_2$), and it was concluded from analysis that it had structure (XVII). Methanolic solutions of the three bases had each a sharp absorption maximum, for which the chain of conjugated double bonds is doubtless responsible.

Tables 1 and 2 contain the absorption maxima of methanolic solutions of the methincyanines and styryl dyes respectively, as well as the shifts which occur on substitution, and the molecular extinction coefficients. A connection between departure from planarity of the molecule and decreased intensity of absorption was deduced with *o*-substituted diphenyls [30] and with certain dimethylanilines.[31] In the cyanine series, intensity of absorption is diminished by substitution on the chain and has been ascribed to non-planarity,[4,5] as also with styryl dyes.[29] All the chain-substituted dyes recorded in the Tables show decreased intensity of absorption.

With the dimethylanilines, non-planarity of the molecule led to absorption at a shorter wavelength.[31] Other instances of absorption at a shorter wavelength due to steric effects have been recorded; [32] even in the cyanine series, four methincyanines, each of which had a 3 : 4-benzoquinoline nucleus and could not have planar molecules,[33] absorbed at a shorter

[28] Bloch and Hamer, *Phot. J.*, 1930, **54**, 374.
[29] Kiprianov and Ushenko, *J. Gen. Chem.* (*U.S.S.R.*), 1950, **20**, 543 (*Zhur. obshchei Khim.*, p. 514).
[30] O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906.
[31] Remington, *ibid.*, 1945, **67**, 1838.
[32] Förster, *Z. Elektrochem.*, 1939, **45**, 548.
[33] Sheppard, Lambert, and Walker, *Nature*, 1940, **145**, 386.

wavelength than the analogues having a 5 : 6-benzoquinoline nucleus.[34] On the other hand, a bathochromic shift of absorption maximum was ascribed to steric deformation with the dipyrrylmethenes [35] and with *N*-methyl*æt*ioporphyrin II.[36] Instances of bathochromic shifts caused by chain-substitution of methincyanines, and attributed to non-planarity of

TABLE 1. *Methincyanines.*

R	Abs. max. (Å)	Bathochromic shift on substn. (Å)	ε	Ref.
Formula (II; R′ = R″ = Et)				
H	4860	—	51,200	*a*, *b*
Me	5450	590	25,900	
Ph	5520	660	31,400	
p-C_6H_4·NO_2	5480 (4500)	620	24,400 (11,560)	
CO_2Et	4780	− 80	10,700	
2-Benzothiazolyl	5470	610	11,500	
Formula (II; R′ = Me, R″ = Et)				
H	4850	—	50,200	*a*
CO_2Et	4750	−100	15,000	
Formula (V; R′ = R″ = Et)				
H	4980	—	50,000	*b*
Me	5470	490	24,200	
Ph	5560	580	25,800	
Formula (VI; R′ = R″ = Et)				
H	5020	—	24,800	*c*
Me	5230	210	5,590	
Ph	5480	460	6,960	
Formula (VII; R′ = R″ = Et)				
H	5030	—	52,600	13, *b*
Me	5770	740	26,000	
Ph	5810	780	31,100	
Formula (IV; R′ = R″ = Et)				
H	4220	—	86,700	*d*
Me	4770	550	40,000	
CO_2Et	4370	150	11,500	
Formula (IV; R′ = Me, R″ = Et)				
H	4220	—	86,500	
CO_2Et	4320	100	21,780	
Formula (XIII; R′ = R″ = Et)				
H	4370	—	53,000	10, *b*
Me	4960	590	24,600	
Ph	5050 (4900 inflexion)	680	30,200 (27,000)	
O-Analogues of (V; R′ = R″ = Et)				
H	4630 (4450)	—	50,300 (49,400)	*b*
Ph	5140	510	27,300	
O-Analogues of (VI; R′ = R″ = Et)				
H	4550	—	28,000	
Ph	5080	530	7,000	
O-Analogues of (VII; R′ = R″ = Et)				
H	4700	—	64,400	*b*, *e*
Ph	5320	620	33,300	

[a] Hamer, *J.*, 1928, 206. [b] Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *A*, **163**, 138. [c] Fisher and Hamer, *J.*, 1934, 1905. [d] *Idem*, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703. [e] O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906.

TABLE 2. *Styryl compounds.*

R	Abs. max. (Å)	Hypsochromic shift on substn. (Å)	ε
Formula (XIV; R′ = Me)			
H	5250 [a]	—	79,000
Me	4600 [a]	650	21,000
Ph	4910 [a]	340	25,300
p-C_6H_4·NO_2	4820	430	28,000
CO_2Et	4180 †	1070	25,000
2-Benzothiazolyl	4380	870	32,800
Formula (XIV; R′ = Et)			
H	5380	—	81,500
Me	4670	710	25,400
Formula (XV; R′ = Me)			
H	4920	—	70,000
Me	4670	250	30,880
Ph	4910	10	58,200

[a] For the corresponding perchlorates (XIV; R′ = Me, R = H, Me, and Ph), Kiprianov and Ushenko [39] give 5300, 4810, and 5080 Å, respectively, but their solvent is not recorded.

† Van Dormael and Nys [8] said that the corresponding methiodide decomposed during recrystallisation, so that $\lambda_{max.}$ could not be determined exactly, but was about 4860 Å.

the molecule, have been recorded.[4, 5] Vittum and Brown [37] pointed out that steric factors may produce sometimes an increase and sometimes a decrease of the wavelength of maximum absorption, depending on their effects on the ground state and on the excited state.

[34] Brooker and Keyes, *J. Amer. Chem. Soc.*, 1936, **58**, 659.
[35] Brunings and Corwin, *ibid.*, 1942, **64**, 593.
[36] Ellingson and Corwin, *ibid.*, 1946, **68**, 1112.
[37] Vittum and Brown, *ibid.*, 1947, **69**, 152.

Table 1 shows that in four instances the bathochromic shift on passing from :CH· to :CMe· varies from 490 to 590 Å, whilst for the *iso*quinoline dye (VI) it is smaller (210 Å) and for the 4-linked quinoline dye (VII) it is larger (780 Å). In six instances, the shift on passing from :CH· to :CPh· varies from 510 to 680 Å, but again is smaller in (VI) (460 Å) and larger in (VII) (780 Å). In each of five instances, substitution of hydrogen by phenyl produces a bigger shift than its substitution by methyl. The *p*-nitrophenyl group causes a rather smaller shift than does the phenyl group, which implies that the effect is not electronic. The large 2-benzothiazolyl group causes a shift which is again a little less. With two pairs represented by (IV), the introduction of the ethoxycarbonyl group produces bathochromic shifts of 150 and 100 Å, respectively. On the other hand, in two pairs represented by (II), the shifts on passing from :CH· to :C(CO_2Et)· are hypsochromic, of 80 and 100 Å. Van Dormael and Nys recorded the absence of shift in a pair represented by (IV), whence they concluded that the two benzothiazole nuclei lie in one plane and the ethoxycarbonyl group in another.[8] However, in making a Courtauld model of the compound (X), of which the dye (IV; R = CO_2Et, R′ = R″ = Et) is the ethiodide, a fairly stable arrangement was attained when the ethoxycarbonyl group and one benzothiazole nucleus lay in one plane and the second benzothiazole nucleus in another.

Although there are hypsochromic shifts on passing from two parent methincyanines represented by (II) to the corresponding *meso*-ethoxycarbonylmethincyanines, and bathochromic shifts on passing from two parent methincyanines represented by (IV) to the corresponding *meso*-ethoxycarbonylmethincyanines, just the opposite occurs, in each instance, on passing to the *meso*-ethoxycarbonyl bases (X) and (XI) from the parent bases. The magnitude of these two shifts cannot be stated, since more than one value of $\lambda_{max.}$ was recorded for each parent base;[38] possibly those different values corresponded with different stereoisomeric forms.

The striking observation that, in the styryl series, substitution on the chain causes a hypsochromic shift of absorption maximum[29] is borne out by the examples in Table 2. Here, in two instances, a change from :CH· to :CMe· in the benzothiazole series caused hypsochromic shifts of 650 and 710 Å, that in the benzoxazole series being smaller (250 Å). In the benzothiazole series the hypsochromic shifts on replacing :CH· by :CR· increase as R represents the groups Ph, *p*-C_6H_4·NO_2, Me, 2-benzothiazolyl, CO_2Et, reaching the figure 1070 Å for the last.

Of nineteen chain-substituted methincyanines that were tested photographically, fourteen had no sensitising action; nine of the eleven unsubstituted parent dyes are strong sensitisers, but not the two containing the *iso*quinoline nucleus.[39] Extremely weak sensitising of a chlorobromide emulsion was shown by the remaining five chain-substituted methincyanines, *viz.*, (IV; R = Me, R′ = R″ = Et), (II; R = CO_2Et, R′ = Me or Et, R″ = Et), and (IV; R = CO_2Et, R′ = Me or Et, R″ = Et).

Of the eight chain-substituted styryl dyes, seven were photographic sensitisers, but weaker than the corresponding unsubstituted dyes, of which there were three. In comparison with the sensitisation by the *meso*-phenyl dye (XIV; R′ = Me, R = Ph), it is interesting that the *p*-nitrophenyl analogue was not a sensitiser and strongly depressed the normal sensitivity of the emulsion.

Experimental

A, Bases and Salts.

Phenylacetyl Chloride.—As the preparation by use of phosphorus pentachloride[40] could not be reproduced, thionyl chloride[41] was used. To boiling thionyl chloride (18 c.c., 1·25 mols.), phenylacetic acid (27·2 g., 1 mol.) was added during 10 min. After a further 30 minutes' boiling, the liquid was distilled. The fraction, b. p. 96—98°/17 mm., comprised a 77% yield.

2-Benzylbenzothiazole.[42]—This was prepared by mixing phenylacetyl chloride (17·80 g., 1 mol.)

[38] Hamer, *J.*, 1940, 799.
[39] Fisher and Hamer, *J.*, 1934, 1905.
[40] Schott, *Ber.*, 1896, **29**, 1985.
[41] Meyer, *Monatsh.*, 1901, **22**, 415.
[42] Hofmann, *Ber.*, 1880, **13**, 1223.

with *o*-aminothiophenol hydrochloride (1 mol.), stirring in phosphoric oxide (0·33 mol.), and heating the mixture in an oil-bath. After 8 min. at 160—175°, the product was warmed with sodium hydroxide solution, and the base extracted with ether. After removal of the solvent from the dried extract, the viscous yellow oil had b. p. 157°/0·5 mm., and the fraction of b. p. 157—163°/0·5 mm. amounted to a 29% yield. Skraup and Böhm [43] recorded b. p. 204—205°/13 mm.

2-*Benzylbenzothiazole Ethiodide*.—2-Benzylbenzothiazole (9·82 g., 1 mol.) and ethyl iodide (1·2 mols.) were heated at 100° for 48 hr. The acetone-treated product (71% yield) was recrystallised from ethanol (7 c.c. per g.), giving a 57% yield. The pale yellow crystals of *ethiodide* had m. p. 181° (Found: C, 50·2; H, 4·4. $C_{16}H_{16}NIS$ requires C, 50·4; H, 4·25%).

p-*Nitrophenylacetic Acid*.—Phenylacetic acid was nitrated by Borsche's method; [44] he records a 50—60% yield of *p*-nitro-compound, m. p. 152°. The present yield of crude acid was 76% but the m. p. was 95—140° and four recrystallisations from water were required (one from 20 c.c. per g. and three from 100 c.c. per g.) for the m. p. to reach 151°, at which point the yield was only 22%.

p-Nitrophenylacetyl chloride, prepared by use of phosphorus pentachloride,[45] had m. p. 47°. In our work, thionyl chloride (10·4 c.c., 3 mols.) was boiled, *p*-nitrophenylacetic acid (8·72 g., 1 mol.) gradually added, and boiling continued for 30 min. Excess of thionyl chloride was distilled off and the residual oil extracted with light petroleum (b. p. 40—60°; 1500 c.c.). The chloride (44% yield) had m. p. 48°. Pyman [46] gives m. p. 48°.

2-4′-*Nitrobenzylbenzothiazole*.—To *p*-nitrophenylacetyl chloride (3·28 g., 1 mol.) and *o*-aminothiophenol (1 mol.) at 115°, phosphoric oxide (1 mol.) was stirred in. After 15 min. at 145—170°, the brown glass was heated with sodium hydroxide solution and benzene. From the dried extract the benzene was removed. The crystalline residue was dissolved in hot ethanol (30 c.c.), and the solution treated with hot water (30 c.c.). The resultant oil solidified (88% yield). After recrystallisation from ethanol (10 c.c. per g.) the yield of sand-coloured *benzothiazole* was 73%, and the m. p. 115°. Another such recrystallisation (17 c.c. per g.) gave a 58% yield, but no change of m. p. (Found: C, 62·05; H, 3·65. $C_{14}H_{10}O_2N_2S$ requires C, 62·15; H, 3·75%).

The thiazole (2·7 g., 1 mol.) and ethyl iodide (1·2 mols.) were heated at 100° for 24 hr. Treatment with acetone (total 30 c.c.) gave a pale yellow salt (88%). This was recrystallised from methanol (100 c.c. per g.), contact with water being avoided, and gave a 67% yield of pale beige *ethiodide*, m. p. 249° (decomp.) with previous darkening (Found: C, 45·05; H, 3·7. $C_{16}H_{15}O_2N_2IS$ requires C, 45·05; H, 3·55%).

Ethoxycarbonylacetyl Chloride.—The method of Staudinger and Becker [47] required modification, possibly because of the present smaller scale. Potassium ethyl malonate (32·49 g., 1 mol.) was gradually added to boiling thionyl chloride (1·25 mols.), and the mixture was further boiled for a few minutes, then, without filtering, distilled. The yield was 64%, and the b. p. 75—78°/21 mm.

2-*Ethoxycarbonylmethylbenzothiazole*.—In a repetition of the method of van Dormael and Nys,[22] a suspension of the zinc salt (20·85 g., 0·5 mol.) of *o*-aminothiophenol in boiling dry benzene (90 c.c.) was treated gradually with ethoxycarbonylacetyl chloride (1 mol.) in dry benzene (120 c.c.); the mixture was boiled for 6 hr., lumps of zinc salt being broken up at intervals. The solid was filtered off hot and boiled out with benzene (2 × 30 c.c.). After being washed with water, it amounted to a 23% recovery of zinc salt. The benzene extract was shaken with excess of aqueous sodium hydrogen carbonate, washed with water, and dried (Na_2SO_4). The solvent was taken off under reduced pressure. Van Dormael and Nys thus obtained a 70% yield of base, which they subjected to condensations. In the present work, the crude product was distilled, giving a pale yellow *base*, b. p. 121—126°/0·5 mm. (Found: C, 59·65; H, 5·05. $C_{11}H_{11}O_2NS$ requires C, 59·7; H, 5·0%). Taking account of the recovered zinc salt, the yield was 53%.

This thiazole (0·64 g., 1 mol.) and methyl iodide (1·25 mols.) were heated in a sealed tube at 65° for 15 hr. and then treated with anhydrous ether and acetone (2 : 1), as described by van Dormael and Nys.[22] The *methiodide* was obtained in their yield (70%), but with much lower m. p. On recrystallisation from methanol–acetone (1 : 3) (16 c.c. per g.), the yield dropped

[43] Skraup and Böhm, *Ber.*, 1926, **59**, 1007.
[44] Borsche, *Ber.*, 1909, **42**, 3596.
[45] Wedekind, Häussermann, Weisswange, and Miller, *Annalen*, 1911, **378**, 261.
[46] Pyman, *J.*, 1917, **111**, 169.
[47] Staudinger and Becker, *Ber.*, 1917, **50**, 1016.

to 28%; the m. p. was 175° (decomp.) with previous darkening (Found: C, 40·05; H, 4·15. $C_{12}H_{14}O_2NIS$ requires C, 39·7; H, 3·9%). Van Dormael and Nys give m. p. 170—171° (decomp.) but do not record the yield at this stage or an analysis. Addition of ether to the filtrate from the recrystallisation precipitated a solid (0·09 g.), which was recrystallised from ethanol (4 c.c.; 0·06 g. obtained). Although this had m. p. 172° (decomp.), a colour-test showed contamination with 2-methylbenzothiazole methiodide.

In an attempted preparation where the reactants were heated at 100° for 24 hr., treatment with dry acetone gave a 54% yield of crystals; after two recrystallisations from ethanol (12 c.c. per g.), the yield was 22%, and the m. p. 210° (decomp.). By the colour-test and by analysis (Found: C, 37·0; H, 3·7. Calc. for $C_9H_{10}NIS$: C, 37·1; H, 3·45%), this salt was identified as 2-methylbenzothiazole methiodide.

2-Ethoxycarbonylmethylbenzothiazole Ethiodide.—(*a*) When 2-ethoxycarbonylmethylbenzothiazole and ethyl iodide were heated in a sealed tube at 65° for 15 hr., salt formation did not occur. The base and ethyl iodide were heated at 100° for 24 hr., the supernatant liquid was poured off, and the gum treated with acetone; a 51% yield of crystals resulted. After two recrystallisations from ethanol (7 c.c. per g.), the yield was 23%; the m. p., 190° (decomp.), was unchanged by the second recrystallisation. From m. p., mixed m. p., analysis (Found: C, 39·4; H, 4·2. Calc. for $C_{10}H_{12}NIS$: C, 39·35; H, 3·95%), and the colour test, the salt was identified as 2-methylbenzothiazole ethiodide.

(*b*) (Cf. Kiprianov and Pazenko.[39]) To a solution of *o*-ethylaminothiophenol (0·81 g., 1 mol.) in dry benzene (4 c.c.) was added one of ethoxycarbonylacetyl chloride (1·1 mols.) in dry benzene (2 c.c.). After cooling to room temperature, the liquid was decanted and the gum washed twice with benzene, dissolved in hot methanol (2 c.c.), and treated with a warm solution of potassium iodide (2 mols.) in water (4 c.c.). The *ethiodide* crystallised and was filtered off and washed (49% yield). After recrystallisation from methanol (5 c.c. per g.), the yield was 32%. The white crystals had m. p. 155° (decomp.), with previous yellowing, but the m. p. depended on the rate of heating (Found: C, 41·55; H, 4·6. $C_{12}H_{16}O_2NIS$ requires C, 41·4; H, 4·3%).

2-Chloromethylbenzothiazole.—Chloroacetyl chloride [48] (8·28 g.; 1 mol.) was cooled with ice, and *o*-aminothiophenol (1 mol.) was gradually stirred in. Phosphoric oxide (0·33 mol.) was added and the mixture heated in an oil-bath. After 45 min. at 140—150°, the product was heated with water, benzene, and sodium hydroxide solution. After repeated benzene extraction, the dark extract was dried (Na_2SO_4). The solvent was taken off and the residue distilled. The *product* (18%), b. p. 79—91°/0·2 mm., solidified. On recrystallisation of this from light petroleum (b. p. 40—60°; 8 c.c. per g.), the yield dropped to 6% and there was a residue. The colourless crystals had m. p. 34° (Found: C, 52·55; H, 3·55. C_8H_6NClS requires C, 52·3; H, 3·3%).

2-(o-Ethylaminophenylthiomethyl)benzothiazole Ethiodide (VIII).—An attempt to prepare 2-chloromethylbenzothiazole ethiodide, by heating the base with ethyl iodide in a sealed tube, was unsuccessful, so Kiprianov and Pazenko's general method [39] was tried. A solution of *o*-ethylaminothiophenol (1·58 g., 1 mol.) in dry benzene (5 c.c.) was treated with one of chloroacetyl chloride (2 mols.) in dry benzene (4 c.c.), with slight cooling. Heat was evolved and a pale yellow solid separated. After cooling, the liquid was decanted and the solid washed twice with dry benzene. It was dissolved in hot methanol (6 c.c.) and the solution was treated with hot aqueous potassium iodide. After cooling, the brown and tacky product was twice washed with water, by decantation, and then treated with acetone (3 c.c.), whereupon a yellow solid separated. This was filtered off and washed with acetone (4 × 1 c.c.). The yield amounted to 19%, but in a preparation on a scale half as large again it was only 11%; another preparation on the larger scale decomposed completely on treatment with potassium iodide. Recrystallisation from methanol (14 c.c. per g.) decreased the 19% yield to 17%, and a second recrystallisation to 13%, but the m. p., 158° (decomp.), was unaltered by the second recrystallisation (Found: C, 47·15; H, 4·65; N, 6·3; I 27·85; S, 14·2. $C_{18}H_{21}N_2IS_2$ requires C, 47·35; H, 4·65; N, 6·15; I, 27·8; S, 14·05%). It was concluded that the *ethiodide* must be that named above. Although the precautions recommended [39] in preparing 2-bromomethylbenzothiazole methobromide were observed, decomposition occurred at the stage of addition of potassium iodide.

3-Ethyl-2-oxobenzothiazoline.—This, b. p. 170°/14 mm., was prepared by Fuchs and Grauaug from 3-ethyl-2-nitrosoiminobenzothiazoline.[49] Hunter [50] described it as an oil. Sexton [51] prepared its 3-methyl homologue from 2-methylthiobenzothiazole methosulphate and alkali.

[48] Barnett, *Chem. News*, 1921, **122**, 220.
[49] Fuchs and Grauaug, *Ber.*, 1928, **61**, *B*, 57.
[50] Hunter, *J.*, 1930, 125.
[51] Sexton, *J.*, 1939, 470.

Kiprianov and Pazenko [52] claim to have prepared similarly the 3-ethyl compound and, by treatment with ligroin, to have obtained it with m. p. 58°. In the present work 2-ethylthiobenzothiazole (19·93 g., 1 mol.) was heated with neutral ethyl sulphate (1 mol.) at 110—120° for 8 hr. Although the gum sometimes crystallised spontaneously, its solution in water (120 c.c.) was cloudy and acid. It was cleared by extraction with ether and was then stirred and cooled with ice during addition of an ice-cold solution of sodium hydroxide (2·2 mols.) in water (40 c.c.). The oil from the dried ether extract (Na_2SO_4) was distilled in a vacuum. The yield varied, in eight experiments, from 30 to 83% (average 53%). An analytically pure sample of the 2-oxo-compound was clear and colourless and had b. p. 101°/0·5 mm. (Found: C, 60·25; H, 5·0. Calc. for C_9H_9ONS: C, 60·3; H, 5·05%), and could not be induced to solidify. When crude, it tends to distil cloudy, which is attributed to contamination by 2-thio-compound since that was isolated by treating the highest-boiling fraction with ether and light petroleum (Found, after two recrystallisation from light petroleum: C, 55·25; H, 4·8. Calc. for $C_9H_9NS_2$: C, 55·35; H, 4·65%); its identity was confirmed by its m. p., 78°, and mixed m. p., and the yield was of the order 6—14%.

3-*Ethyl*-2-*thiobenzothiazoline*.—This was originally prepared, with m. p. 75°, by heating 3-ethyl-2-nitrosoiminobenzothiazoline with phosphorus pentasulphide,[50] secondly, with m. p. 78—79°, by refluxing 2-ethylthiobenzothiazole ethotoluene-*p*-sulphonate with pyridine and pouring into water,[53] and thirdly, with m. p. 73—75°, by heating 2-ethylthiobenzothiazole with iodine.[52] On repetition of the second method, 2-ethylthiobenzothiazole (19·5 g., 1 mol.) and ethyl sulphate (1 mol.) were heated together at 110—120° for 8 hr. A solution of the salt in pyridine (100 c.c.) was boiled for an hour, then poured into warm water (1 l.). The washed thione (93% yield) was recrystallised from methanol (3 c.c. per g.), giving an 82% yield (m. p. 77—78°). In another experiment, freshly prepared 2-ethylthiobenzothiazole ethiodide (0·63 g.) was boiled with pyridine (3 c.c.) for 10 min. and the solution poured into water (12 c.c.). On recrystallisation of the product (83%) from light petroleum (b. p. 60—80°; 25 c.c. per g.), the yield dropped to 68%. This material had m. p. 78° (Found: C, 55·2; H, 4·7. Calc. for $C_9H_9NS_2$: C, 55·35; H, 4·65%).

2-*Ethylthiobenzothiazole Ethiodide*.—When a sample which had been prepared some months previously was converted by pyridine into the thione, the impossibly high yield led to the conclusion that partial conversion had already occurred. Calculated from the carbon content (Found: C, 48·3; H, 4·4. Calc. for $C_{11}H_{14}NIS_2$: C, 37·6; H, 4·0%. Calc. for $C_9H_9NS_2$: C, 55·35; H, 4·65%), the proportion of ethiodide was 40% and of thione 60%. A similar sample of ethiodide (2 g.) was thrice ground with anhydrous benzene (3 × 5 c.c.). The residue of ethiodide amounted to 28%, whilst the quantity of thione obtained on removal of the benzene was 64%; after recrystallisation from light petroleum it was 56% (m. p. 78°). This deterioration of the ethiodide may explain why alkiodides appeared less satisfactory for preparation of dye bases than did alkotoluene-*p*-sulphonates.[53]

o-*Ethylaminothiophenol*.—This, b. p. 129—130°/20 mm., was prepared from crude 3-ethyl-2-oxobenzothiazoline by boiling with alcoholic potassium hydroxide and the yield, based on the quaternary salt used for making the 2-oxo-compound, was claimed [53] to be 73%. On repetition, only a 47% yield was obtained, perhaps owing to the variability of crude 2-oxo-compound. Preferably distilled 2-oxo-compound (12·10 g., 1 mol.), in ethanol (24 c.c.), was boiled with a solution of potassium hydroxide (6 mols.) in ethanol (70 c.c.) for 1 hr. After cooling, the potassium carbonate was filtered off and washed with ethanol, and the filtrate and washings were evaporated to dryness. The residue was dissolved in water (100 c.c.), and the solution was cooled during addition of concentrated hydrochloric acid. The precipitated oil was extracted with benzene, and the extract dried (Na_2SO_4). After removal of solvent, the yield of pale yellow oil, b. p. 57—60°/0·5 mm., was 77% (Found: C, 62·8; H, 7·3. Calc. for $C_8H_{11}NS$: C, 62·7; H, 7·25%).

This compound is better prepared from 3-ethyl-2-thiobenzothiazoline, since the preparation of that is straightforward. Thus this 2-thione (19·53 g., 1 mol.), in ethanol (40 c.c.), was boiled with potassium hydroxide (6 mols.) in ethanol (105 c.c.) for 6 hr. After cooling, the solid was filtered off and washed with ethanol, and the filtrate and washings were concentrated to a paste. This was treated with water (130 c.c.), and the solution was extracted with benzene and neutralised with hydrochloric acid. The oil was extracted with benzene. The yield was 70%, and the b. p. 56—64°/0·4 mm. Kiprianov and Pazenko [53] claimed 77%. When only 4 mols. of

[52] Kiprianov and Pazenko, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 1523.
[53] Kendall, B.P. 475,647/1936.

potassium hydroxide were used, there was a 24% recovery of thione, which was filtered off with the potassium salt and freed from it by washing with water.

2-Ethylbenzoxazole.—By a procedure similar to that for 2-methylbenzoxazole,[54] *o*-aminophenol (42·6 g., 1 mol.) was gradually added to propionic anhydride (3 mols.). The liquid was heated on a water-bath for 30 min. and then in an oil-bath, to remove propionic acid and anhydride. The latter fraction, b. p. 150—168°, and the residue were distilled under a vacuum. The distillate was subjected to prolonged treatment with 10% sodium carbonate solution, extracted with ether, and redistilled, giving a 28% yield of material, b. p. 40—43°/0·3—0·5 mm. Skraup and Moser,[55] who prepared it from *o*-aminophenol and propionitrile under pressure, give b. p. 210°.

2-Ethylbenzoxazole (16·25 g.) and ethyl iodide were heated together at 100° for 8 hr. After treatment with anhydrous acetone (40 c.c.), the yield was 58%. Recrystallisation from ethanol (3 c.c. per g.) gave a 40% yield of colourless *ethiodide*, m. p. 198° (decomp.) (Found: C, 43·5; H, 4·85. $C_{11}H_{14}ONI$ requires C, 43·55; H, 4·65%).

2-Benzylbenzoxazole.[56]—Prepared from *o*-aminophenol and benzyl cyanide, this had b. p. 325°/750 mm. According to the present method, *o*-aminophenol (10·9 g., 1 mol.) and phenylacetic acid (1 mol.) were heated for 3 hr. at 200—225°, in a flask allowing the escape of water vapour. The product was treated with aqueous sodium hydroxide and extracted with benzene, which gave a yellowish oil, b. p. 118—125°/0·3 mm. (48%).

An attempt to prepare the ethiodide at 100° was unsuccessful. The ethotoluene-*p*-sulphonate was prepared as a gum, which was dissolved by dry acetone (1 c.c. per g.), instead of being induced to solidify; it was used for dye condensations.

B, Methincyanine Dyes.

[2-(3-Ethylbenzothiazole)][2-(1-ethylquinoline)]methylmethincyanine Iodide (II; R = Me, R′ = R″ = Et).—To 2-ethylbenzothiazole ethiodide (0·80 g., 1 mol.) and 2-iodoquinoline ethiodide (1 mol.) in ethanol (3 c.c.), triethylamine (2·1 mols.) was added and the mixture was boiled and stirred for 1 min. Ether precipitated a tar, which was washed with ether and then crystallised from hot acetone (4 c.c.). The yield of acetone-washed dye was 72% and a chromatogram with chloroform on alumina gave no indication of coloured by-product. After recrystallisation from ethanol (7 c.c. per g.), the olive-green *dye* (54%) melted about 148°, with softening from 125° (Found: C, 55·45; H, 5·35. $C_{22}H_{22}N_2IS$ requires C, 55·65; H, 4·9%). Towards a photographic emulsion the dye had a slight desensitising action.

With 30 minutes' heating, the yields were 84% and 59%, and again no dye by-product was detected. In a similar experiment with 2-ethylbenzothiazole ethotoluene-*p*-sulphonate, with heating for 1 min., the tar precipitated by ether was heated with aqueous potassium iodide. After cooling, the liquid was decanted and the tar heated with acetone, giving a 66% yield, which dropped to 48% on recrystallisation. Götze obtained two dyes by condensation of 2-ethylbenzothiazole ethiodide with 2-iodoquinoline methiodide,[3] but the present products were homogeneous.

On the other hand, when 2-ethylbenzothiazole ethiodide (0·80 g., 1 mol.), 2-ethylthioquinoline ethiodide (1 mol.), ethanol (5 c.c.), and triethylamine (1·1 mols.) were boiled together for 10 min., the dye precipitated by ether, washed with water, and obtained in 30% yield by boiling with acetone (6 c.c.) was a mixture. By chromatography with chloroform, containing ethanol (1%), on alumina, the chain-substituted purple dye was washed through; the extract was concentrated in a vacuum and the residue, on treatment with acetone, gave a 12% yield (3% on recrystallisation from ethanol). The alumina from the upper part of the column was extracted with hot methanol, and the extract taken to dryness and treated with acetone. The residue (0·005 g.) had the same m. p. and mixed m. p. as had [2-(3-ethylbenzothiazole)][2-(1-ethylquinoline)]methincyanine iodide (II; R = H, R′ = R″ = Et); also the absorption maxima of their methanolic solutions were identical.

Bis-2-(3-ethylbenzothiazole)methylmethincyanine Iodide (IV; R = Me, R′ = R″ = Et, X = I).—To a hot solution of 2-ethylbenzothiazole ethiodide (1·60 g., 1 mol.) and 2-ethylthiobenzothiazole ethiodide (1 mol.) in ethanol (20 c.c.) was added triethylamine (1·1 mols.) and the whole was boiled for 35 min. The mixture of salts and dyes, precipitated by ether, was ground with water, whereby the dyes were left in 16% yield (0·38 g.). They were boiled out with ethanol

[54] Phillips, *J. Soc. Chem. Ind.*, 1937, **56**, 474T.
[55] Skraup and Moser, *Ber.*, 1922, **55**, 1080.
[56] Skraup, *Annalen*, 1919, **419**, 1.

(8 c.c.), which left a yellow residue (0·08 g.). The filtrate was boiled with charcoal (0·04 g.), then refiltered, and from it the desired dye separated in 8% yield. It recrystallised from ethanol (20 c.c. per g.; charcoal) in 5% yield. The brick-red *cyanine* had m. p. about 214° (decomp.), with previous darkening and shrinking (Found: C, 50·15; H, 4·75. $C_{20}H_{21}N_2IS_2$ requires C, 50·0; H, 4·4%). The dye was inert in a bromoiodide photographic emulsion but sensitised a chlorobromide emulsion extremely weakly to 5400 Å. It has been claimed [57] that this condensation is effected with sodium ethoxide in 24% yield, dropping on recrystallisation to 13% (m. p. 232°).

The yellow residue was recrystallised from methanol (250 c.c. per g.; 0·06 g. obtained). By m. p., mixed m. p., and identity of absorption maxima, it was established as bis-2-(3-ethylbenzothiazole)methincyanine iodide (IV; R = H, R′ = R″ = Et, X = I).

[2-(3-*Ethylbenzothiazole*)][2-(1-*ethylquinoline*)]*phenylmethincyanine Iodide* (II; R = Ph, R′ = R″ = Et).—2-Benzylbenzothiazole ethiodide (0·95 g., 1 mol.), 2-iodoquinoline ethiodide (1 mol.), ethanol (5 c.c.), and triethylamine (2·1 mols.), boiled and stirred for 3 min., gave a 79% yield of washed dye. Recrystallisation from ethanol (25 c.c. per g.) gave a 60% yield (Found: C, 60·15; H, 4·7. $C_{27}H_{25}N_2IS$ requires C, 60·4; H, 4·7%). The *dye* strongly desensitised a bromoiodide photographic emulsion.

[2-(1-*Ethyl*-5 : 6-*benzoquinoline*)][2-(3-*ethylbenzothiazole*)]*methincyanine Iodide* (V; R = H, R′ = R″ = Et).—2-Methylbenzothiazole ethiodide (3·05 g.) and 2-iodo-5 : 6-benzoquinoline ethiodide in ethanol (120 c.c.) with triethylamine were boiled and stirred for 30 min. The washed dye (68% yield) was obtained in a 42% yield after two recrystallisations from methanol (170 c.c. per g.) (Found: I, 24·9. Calc. for $C_{23}H_{23}N_2IS$: I, 24·85%). The reddish-orange crystals had m. p. 258° (decomp.).

[2-(1-*Ethyl*-5 : 6-*benzoquinoline*)][2-(3-*ethylbenzothiazole*)]*methylmethincyanine Iodide* (V; R = Me, R′ = R″ = Et).—2-Ethylbenzothiazole ethiodide (0·80 g.), 2-iodo-5 : 6-benzoquinoline ethiodide, ethanol (8 c.c.), and triethylamine were boiled together for 15 min. From the hot filtrate, the *dye* crystallised in 89% yield and was obtained in 67% yield after recrystallisation from ethanol (70 c.c. per g.). The dark purplish crystals underwent violent decomposition at about 225° (Found: C, 59·15; H, 4·95. $C_{26}H_{25}N_2IS$ requires C, 59·55; H, 4·8%). The substance strongly desensitised a bromoiodide photographic emulsion.

[2-(1-*Ethyl*-5 : 6-*benzoquinoline*)][2-(3-*ethylbenzothiazole*)]*phenylmethincyanine Iodide* (V; R = Ph, R′ = R″ = Et).—By use of 2-benzylbenzothiazole ethiodide (0·95 g.) instead of 2-ethylbenzothiazole ethiodide above, the product separated as tar, which eventually crystallised. The washed *dye* (58% yield) was recrystallised from ethanol (15 c.c. per g.) and obtained in 42% yield. The purple crystals had m. p. about 175° (decomp.) (Found: C, 63·3; H, 4·8. $C_{31}H_{27}N_2IS$ requires C, 63·45; H, 4·65%). The dye slightly desensitised a chlorobromide and a bromoiodide emulsion.

[2-(3-*Ethylbenzothiazole*)][1-(2-*ethyl*isoquinoline)]*methylmethincyanine Perchlorate* (VI; R = Me, R′ = R″ = Et, X = ClO_4).—A mixture of 2-ethylbenzothiazole ethiodide (0·80 g.), 1-iodo-*iso*quinoline ethiodide, ethanol (3 c.c.), and triethylamine, boiled for 3 min., gave a purple filtrate and no residue. Ether precipitated the dye iodide as tar, which was washed with ether and with water. Its solution in hot ethanol gave with hot aqueous sodium perchlorate an 89% yield of washed *dye perchlorate*. After recrystallisation from ethanol (20 c.c. per g.), the yield was 72%. The vermilion crystals had m. p. about 164° (decomp.), with previous softening (Found: C, 59·0; H, 5·5. $C_{22}H_{23}O_4N_2ClS$ requires C, 59·1; H, 5·2%). The dye slightly desensitised a chlorobromide and a bromoiodide emulsion.

[2-(3-*Ethylbenzothiazole*)][1-(2-*ethyl*isoquinoline)]*phenylmethincyanine Iodide* (VI; R = Ph, R′ = R″ = Et, X = I).—When the 2-ethylbenzothiazole ethiodide above was replaced by 2-benzylbenzothiazole ethiodide (0·95 g.), the reaction mixture very slowly deposited crystals, the yield of washed dye iodide being 79% (1·06 g.). Half the product was dissolved in chloroform (5 c.c.) and subjected to chromatography on alumina with chloroform. A blue impurity was washed through first, with loss of some purple dye, and the desired purple dye was then extracted from the column with methanol. Concentration gave a 45% yield. Recrystallisation from ethanol (10 c.c. per g.) gave a 36% yield. The maroon crystals partly melted at 135° when quickly heated, with violent decomp. at about 227° (Found: C, 60·65; H, 4·8. $C_{27}H_{25}N_2IS$ requires C, 60·4; H, 4·7%). The *dye* slightly desensitised a chlorobromide and a bromoiodide emulsion.

[2-(3-*Ethylbenzothiazole*)][4-(1-*ethylquinoline*)]*methylmethincyanine Iodide* (VII; R = Me,

[57] Kendall, Fry, and Ilford Ltd., B.P. 660,408/1949.

R′ = R″ = Et).—2-Ethylbenzothiazole ethotoluene-*p*-sulphonate (0·91 g.), 4-iodoquinoline ethiodide, and ethanol, with triethylamine were boiled for 2 min., then treated with hot aqueous potassium iodide. With acetone the tar gave a 56% yield of crystals. Chromatography with chloroform on alumina on a test portion revealed no dye other than the blue one. Recrystallisation from ethanol (6 c.c. per g.) reduced the yield to 49%. The olive-green crystals had m. p. 185° (decomp.) (Found : I, 26·7; S, 6·6. $C_{23}H_{23}N_2IS$ requires I, 26·75; S, 6·75%). The *dye* slightly desensitised a chlorobromide and a bromoiodide photographic emulsion.

In an attempted preparation by a modified thia-4′-cyanine condensation, 2-ethylbenzothiazole ethiodide (1·60 g., 1 mol.) and quinoline ethiodide (3 mols.), dissolved in ethanol (35 c.c.), were boiled with potassium hydroxide (3 mols.) in ethanol (20 c.c.) for 30 min. The washed product amounted to a 14% yield of *apo*cyanines. These were boiled with ethanol (25 c.c.) and the residue was washed with hot ethanol (5 c.c.). From the filtrate and washings there separated an 8% yield, which had the same m. p. and mixed m. p. as erythro*apo*cyanine, and the absorption maxima were the same. The undissolved residue, after recrystallisation from ethanol (35 c.c.), amounted to a ½% yield; like xantho*apo*cyanine, it and their mixture all darkened below 100° but remained unmelted at 300°, and the absorption maxima were the same.

[3-(1-*Ethylquinoline*)][4-(1-*ethylquinoline*)]*cyanine Iodide* (*Erythro*apo*cyanine*).—On reaction of methanolic potassium hydroxide with quinoline ethiodide,[15,16] the yield of crude, washed *apo*cyanines was in our work 31%. They were boiled with ethanol four times (each, 6 c.c. per g.). The residue was recrystallised from ethanol and gave a ½% yield of xantho*apo*cyanine. The crystalline product obtained from the extracts and by their concentration amounted to 20% of erythro*apo*cyanine. Recrystallisation from ethanol (23 c.c. per g.) with charcoal (0·1 g. per g.) reduced the yield to 14%, and a further two recrystallisations from methanol (20 c.c. per g.; charcoal) to 6% (a chromatogram with chloroform on alumina showed no yellow contaminant) (Found : C, 59·8; H, 5·5. Calc. for $C_{23}H_{23}N_2I$: C, 59·7; H, 5·25%). The m. p. was 215—220° (decomp.). The absorption maximum of a methanolic solution was at 5160 Å (ε 31,600). A chlorobromide emulsion was very weakly sensitised to about 6000 Å, whilst a bromoiodide emulsion was slightly desensitised.

[2-(1-*Ethylquinoline*)][3-(1-*ethylquinoline*)]*cyanine Iodide* (*Xantho*apo*cyanine*).—Kaufmann and Strübin [15] said that, by modified conditions, the yield of xantho*apo*cyanine may be increased to 15%. To reproduce this, quinoline ethiodide (7 g., 2 mols.) in ethanol (140 c.c.) was treated with sodium (1·2 atom-equivs.) dissolved in ethanol (20 c.c.), and the solution was boiled for 1 hr. The yield of washed dye was 20%. Recrystallisation from methanol (200 c.c. per g.) gave a 5% yield of orange crystals, which remained unmelted at 305° (Found : C, 59·7; H, 5·5. Calc. for $C_{23}H_{23}N_2I$: C, 59·7; H, 5·25%). Kaufmann and Strübin give m. p. 320° (decomp.). The maxima of a methanolic solution were at 4610 (ε 19,900) and 3620 Å (ε 6200). A chlorobromide emulsion was weakly sensitised, with maxima at 5200 and 5400 Å and a bromoiodide emulsion showed a very weak extension of sensitivity.

[2-(3-*Ethylbenzothiazole*)][4-(1-*ethylquinoline*)]*phenylmethincyanine Iodide* (VII; R = Ph, R′ = R″ = Et).—To a mixture of 2-benzylbenzothiazole ethiodide (1·91 g., 1 mol.) and 4-iodoquinoline ethiodide in ethanol (20 c.c.) was added anhydrous potassium carbonate (180-mesh; 2·1 mols.), and the mixture was boiled for 2 min. The yield of washed *dye* was 99%; after one recrystallisation from ethanol (19 c.c. per g.) and a second from methanol (25 c.c. per g.), it was 56% (Found : I, 23·65; S, 5·8. $C_{27}H_{25}N_2IS$ requires I, 23·65; S, 6·0%). The m. p. was about 222° (decomp.). It desensitised a bromoiodide emulsion without sensitising.

[2-(3-*Ethylbenzothiazole*)][2-(1-*ethylquinoline*)]-p-*nitrophenylmethincyanine Iodide* (II; R = *p*-C_6H_4·NO_2, R′ = R″ = Et).—*p*-Nitrobenzylbenzothiazole (0·54 g., 1 mol.) and ethyl toluene-*p*-sulphonate (1 mol.) were heated together at 165—175° for 4 hr. The gum resulting was dissolved in hot ethanol (8 c.c.), treated with powdered 2-iodoquinoline ethiodide and triethylamine, and boiled for 2 min. Hot filtration removed a little 2-iodo-salt, and two washings with ethanol were given. The tar deposited was treated with ether, then dissolved in hot methanol (10 c.c.) and treated with hot aqueous potassium iodide. The tar hardened and was washed with water, and dried in a vacuum-desiccator (0·58 g. obtained, 40% yield). It was purified by two chromatograms. In the first it was treated with chloroform containing ethanol (1%) on alumina and this gave incomplete removal of a brown forerun; the purplish dye was then collected (23% yield), leaving three coloured impurities in the column. In the second chromatogram, pure chloroform was used to remove a brown forerun; the dye was then washed out (13% yield) with chloroform containing ethanol (1%). Its solution in hot ethanol (6 c.c.), with ether (45 c.c.), gave a 6% yield. Recrystallisation from ethanol (28 c.c. per g.) reduced the yield to 3%. The dark purple crystals had m. p. 216° (decomp.) (Found : C, 55·6; H, 4·5.

$C_{27}H_{24}O_2N_2IS$ requires C, 55·75; H, 4·15%). The *dye* strongly desensitised a bromoiodide emulsion.

Ethoxycarbonylmethin[*2-benzothiazole*][2-(*1-ethyldihydroquinoline*)] (X).—2-Ethylthioquinoline (0·95 g.) and ethyl sulphate were heated together at 110—120° for 8 hr. The salt was dissolved in hot ethanol (5 c.c.), and 2-ethoxycarbonylmethylbenzothiazole (1 mol.) and then triethylamine (2·2 mols.) were added. After 5 minutes' boiling the solution was acidified with hydrochloric acid and treated with sodium perchlorate in hot water (50 c.c.). After cooling, the liquid was decanted from the orange tar. This was washed by melting under hot water, cooling, and decantation. On a second treatment with hot water, the tar did not melt and, after cooling, the solid was filtered off. Whilst still wet, it was dissolved in hot methanol (15 c.c.). A red *perchlorate* crystallised in 66% yield [56% after recrystallisation from methanol (17 c.c. per g.)], and had m. p. 195° (decomp.) (Found: C, 55·6; H, 4·65; N, 5·8. $C_{22}H_{21}O_6N_2ClS$ requires C, 55·4; H, 4·45; N, 5·9%). The perchlorate was ground with water and with aqueous sodium hydroxide. The *base* was extracted with benzene and the extract dried (Na_2SO_4). After removal of solvent, the residue (54%) was taken up in hot benzene (14 c.c.), and the filtered solution treated with hot light petroleum (b. p. 60—80°; 28 c.c.). The yield of almost black crystals was 51% [m. p. 179° (decomp.)] (Found: C, 70·05; H, 5·4. $C_{22}H_{20}O_2N_2S$ requires C, 70·15; H, 5·35%). The absorption maximum of a methanolic solution containing ammonia was at 5170 Å (ε 13,500). A methanolic solution containing sulphuric acid had its maxima at 3290 (ε 41,500) and 4780 Å (ε 8100). The substance sensitised a chlorobromide emulsion extremely weakly.

The base was also prepared by fusing 2-ethylthioquinoline ethotoluene-*p*-sulphonate with 2-ethoxycarbonylmethylbenzothiazole but, under these conditions, was liable to break down partly to the corresponding unsubstituted base.

Ethoxycarbonylmethin[*2-benzothiazole*][2-(*3-ethyl-2 : 3-dihydrobenzothiazole*)] (XI).—2-Ethylthiobenzothiazole (0·98 g.) and ethyl sulphate were heated together at 110—120° for 8 hr., the resulting salt in ethanol was similarly boiled with 2-ethoxycarbonylmethylbenzothiazole and triethylamine, and the product was converted into the yellow *perchlorate* [79% yield; 66% after recrystallisation from methanol (30 c.c. per g.)], m. p. 137° (decomp.) (Found: C, 48·7; H, 4·5; N, 5·75. $C_{20}H_{19}O_6N_2ClS_2,\frac{1}{2}H_2O$ requires C, 48·8; H, 4·1; N, 5·7%).

The derived pale yellow *base* (65% yield), which was recrystallised from benzene (8 c.c. per g.) with light petroleum (b. p. 60—80°; 16 c.c. per g.), had m. p. 127° (47% yield) (Found: C, 62·9; H, 4·8. $C_{20}H_{18}O_2N_2S_2$ requires C, 62·8; H, 4·75%). The absorption maximum of a methanolic solution containing ammonia was at 3430 Å (ε 17,500). That of a methanolic solution containing sulphuric acid was at 4230 Å (ε 9110). The base sensitised a chlorobromide emulsion extremely weakly and was inert towards a chloride emulsion.

It was also prepared by the fusion method, which was less reliable.

[2-(*1-Ethylquinoline*)][2-(*3-methylbenzothiazole*)]*ethoxycarbonylmethincyanine Iodide* (II; R = CO_2Et, R′ = Me, R″ = Et).—Ethoxycarbonylmethin[2-benzothiazole][2-(1-ethyldihydroquinoline)] (0·38 g., 1 mol.) and methyl iodide (1·5 mols.) were heated at 100° for 24 hr. After four extractions with hot benzene (4 × 8 c.c.), the residue of salt amounted to a 59% yield. To remove dye hydriodide, it was shaken with benzene and aqueous sodium hydrogen carbonate (42% yield of residue). The recovery of crude base was 26% at the original benzene extraction and 13% at the second. After two recrystallisations of the *dye* from methanol (9 c.c. per g.), the yield was 25%. The red crystals had m. p. 206° (decomp.) (Found: C, 53·05; H, 4·65; O, 6·4; N, 5·2. $C_{25}H_{23}O_2N_2IS$ requires C, 53·3; H, 4·45; O, 6·15; N, 5·4%). In a chlorobromide emulsion the substance produced extremely weak sensitisation to 5400 Å and very slightly desensitised a bromide emulsion.

[2-(*3-Ethylbenzothiazole*)][2-(*1-ethylquinoline*)]*ethoxycarbonylmethincyanine Iodide* (II; R = CO_2Et, R′ = R″ = Et).—Ethoxycarbonylmethin[2-benzothiazole][2-(1-ethyldihydroquinoline)] (0·75 g., 1 mol.) and ethyl iodide (2 mols.) were heated at 100° for 48 hr. After extraction with hot benzene (4 × 10 c.c.), the residue (77%) was shaken with benzene and sodium hydrogen carbonate solution (58% yield); the ethiodide was taken up in hot methanol (2 c.c.) and the solution treated with hot water (2 c.c.). The yield of crystals was 43%, and after a second such treatment was 32%. The orange *iodide* had m. p. 190° (decomp.) (Found: C, 54·05; H, 4·9. $C_{24}H_{25}O_2N_2IS$ requires C, 54·15; H, 4·75%). The dye produced extremely weak sensitisation of a chlorobromide emulsion and very slight desensitisation of a bromoiodide emulsion.

[2-(*3-Ethylbenzothiazole*)][2-(*3-methylbenzothiazole*)]*methincyanine Iodide* (IV; R = H, R′ = Me, R″ = Et, X = I).—2-Ethylthiobenzothiazole (0·98 g.) was heated with ethyl sulphate, and 2-methylbenzothiazole with methyl toluene-*p*-sulphonate, at 110—120° for 8 hr. A solution of

the salts in hot ethanol (10 c.c.), with triethylamine (2·2 mols.), was boiled for 15 min., then added to hot aqueous potassium iodide. The washed dye iodide was heated with acetone (20 c.c.), cooled, filtered off, and further washed with acetone (yield 72%). The dye was boiled with methanol (20 c.c.) and recrystallised from it (250 c.c.). The yield was 52% and after a second recrystallisation from methanol (150 c.c. per g.) was 41%. The salt was purified by heating it with potassium iodide in aqueous ethanol (40% yield), then further recrystallised from ethanol (280 c.c. per g.) (33% yield). The pale yellow crytals had m. p. 287° (decomp.) (Found: C, 47·8; H, 4·0. Calc. for $C_{18}H_{17}N_2IS_2$: C, 47·8; H, 3·8%). In a chlorobromide emulsion the sensitising maximum was at 4700 Å, the strong sensitisation extending to 5100 Å. Kiprianov and Grigor'eva [58] prepared this dye from 2-methylthiobenzothiazole methiodide, 2-methylbenzothiazole ethiodide, and sodium acetate in alcohol and give m. p. 270·5°.

[2-(3-*Ethylbenzothiazole*)][2-(3-*methylbenzothiazole*)]*ethoxycarbonylmethincyanine Iodide* (IV; R = CO_2Et, R′ = Me, R″ = Et, X = I).—Ethoxycarbonylmethin[2-benzothiazole][2-(3-ethyl-2 : 3-dihydrobenzothiazole)] (0·38 g., 1 mol.) and methyl iodide (1·5 mols.) were heated at 100° for 24 hr. The 40% yield, insoluble in hot benzene, fell to 35% on treatment of the *product* with benzene and sodium hydrogen carbonate solution. Recrystallisation from methanol (28 c.c. per g.) further decreased it to 25%. The pale yellow crystals had m. p. 224° (decomp.) (Found: C, 48·0; H, 4·15; O, 6·1. $C_{21}H_{21}O_2N_2IS_2$ requires C, 48·1; H, 4·05; O, 6·1%). In a chlorobromide or bromoiodide emulsion there was an extremely weak extension of the sensitivity.

[*Bis*-2-(3-*ethylbenzothiazole*)]*ethoxycarbonylmethincyanine Iodide* (IV; R = CO_2Et, R′ = R″ = Et, X = I).—Ethoxycarbonylmethin[2-benzothiazole][2-(3-ethyl-2 : 3-dihydrobenzothiazole)] (0·765 g., 1 mol.) and ethyl iodide (2 mols.) were heated at 100° for 48 hr. Treatment with hot benzene, followed by benzene and sodium hydrogen carbonate solution, left an 80% yield, reduced to 45% on two recrystallisations from methanol (12 c.c. per g.). The yellow *iodide* had m. p. 218° (decomp.), with previous darkening (Found: C, 49·15; H, 4·1. $C_{22}H_{23}O_2N_2IS_2$ requires C, 49·05; H, 4·3%). There was an extremely weak extension of photographic sensitivity, as with the preceding dye.

[2-(3-*Ethylbenzothiazole*)][2-(1-*ethylquinoline*)](2-*benzothiazolyl*)*methincyanine Iodide* (XII).—A mixture of dibenzothiazolylmethane ethiodide (1·10 g.), 2-iodoquinoline ethiodide, ethanol (10 c.c.), and triethylamine was boiled for 30 min. The *dye*, precipitated by ether and washed, was in 38% yield. A chromatogram, with chloroform on alumina, showed it to be homogeneous. Twice recrystallised from methanol (35 c.c. per g.) (yield 20%), the purple crystals had m. p. 232° (decomp.) (Found: C, 56·4; H, 4·35. $C_{26}H_{24}N_2IS_2$ requires C, 56·65; H, 4·1%). The dye caused slight desensitisation of a chlorobromide and a bromoiodide emulsion.

[2-(3-*Ethylbenzoxazole*)][2-(1-*ethylquinoline*)]*methincyanine Iodide* (XIII; R = H, R′ = R″ = Et).—2-Iodoquinoline ethiodide (0·82 g.), 2-methylbenzoxazole ethiodide, ethanol (4 c.c.), and triethylamine were boiled together for 3 min. The yield of washed dye was 33%, whereas a 56% yield had been claimed for 10 minutes' boiling.[10] After two recrystallisations of our product from ethanol (70 c.c. per g.; charcoal), the yield was 15%. The yellow crystals had m. p. 277° (decomp.) [Brooker and Keyes gave m. p. 290—292° (decomp.)] (Found: C, 56·7; H, 4·95. Calc. for $C_{21}H_{21}ON_2I$: C, 56·75; H, 4·75%).

[2-(3-*Ethylbenzoxazole*)][2-(1-*ethylquinoline*)]*methylmethincyanine Iodide* (XIII; R = Me, R′ = R″ = Et).—2-Ethylbenzoxazole ethiodide (3·03 g.), 2-iodoquinoline ethiodide, ethanol (25 c.c.), and triethylamine were boiled for 1 min. The blood-red solution was filtered hot from unchanged iodo-salt, which was washed with hot ethanol (3 c.c.). The filtrate and washings were treated with ether (280 c.c.); the ether-washed tar, dissolved in hot methanol (6 c.c.), was treated with potassium iodide (4 mols.) in hot water (66 c.c.). The tar was washed with water and dried in a vacuum-desiccator (25% yield). The crude dye was chromatographed with chloroform containing 1% of ethanol, on alumina. The blood-red dye was collected first (22% yield), leaving five coloured impurities in the column. The chromatogram was repeated with pure chloroform: this time there was a yellow forerun, then the red dye came through (17% yield). Two recrystallisations from ethanol [4 c.c. (charcoal) and 10 c.c. per g., respectively] reduced the yield to 3%. The maroon crystals shrank suddenly at 110° and decomposed violently at 133° (Found: C, 57·6; H, 5·5. $C_{22}H_{22}ON_2I$ requires C, 57·6; H, 5·05%). The *dye* is very unstable and not all preparations succeeded; a crystalline sample had changed to tar after seven months.

[2-(3-*Ethylbenzoxazole*)][2-(1-*ethylquinoline*)]*phenylmethincyanine Iodide* (XIII; R = Ph, R′ = R″ = Et).—2-Benzylbenzoxazole (0·65 g.) was heated with ethyl toluene-*p*-sulphonate at

[58] Kiprianov and Grigor'eva, *Chem. Abs.*, 1940, **34**, 3274.

150—165° for 4 hr. To the crude salt were added 2-iodoquinoline ethiodide, ethanol (7 c.c.), and triethylamine, and the mixture was boiled for 2 min. The red solution was treated whilst hot with one of potassium iodide (4 mols.) in water (14 c.c.). The water-washed product (1·03 g.) was recrystallised from ethanol (20 c.c.; with charcoal). The yield of dark maroon crystals was 26% (Found: C, 62·1; H, 5·0. $C_{27}H_{25}ON_2I$ requires C, 62·3; H, 4·85%). A chromatogram with chloroform on alumina did not show any coloured by-product. The *dye*, m. p. 227° (decomp.) with previous shrinking, had a slight desensitising effect on a bromoiodide emulsion.

[2-(1-*Ethyl*-5 : 6-*benzoquinoline*)][2-(3-*ethylbenzoxazole*)]*methincyanine Iodide.*—2-Methyl-5 : 6-benzoquinoline (1·93 g., 1 mol.), 2-ethylthiobenzoxazole (1 mol.), and ethyl toluene-*p*-sulphonate (2 mols.) were heated together at 150—160° for 3½ hr. The gum was dissolved in hot alcohol (15 c.c.) and treated with potassium iodide (4 mols.) in hot water (30 c.c.). The resultant oil solidified and was washed with water. After treatment with cold acetone (20 c.c.), the residue amounted to a 34% yield [17% after two recrystallisations from methanol (75 c.c. per g.)]. The orange dye had m. p. 275° (decomp.), with previous shrinking (Found: C, 59·05; H, 5·05; I, 24·05. Calc. for $C_{25}H_{23}ON_2I,CH_3{\cdot}OH$: C, 59·3; H, 5·15; I, 24·15%). Although the recorded absorption maximum is 4450 Å (ref. *b*, Table 1), the values now found are 4630 (ε 50,300) and 4450 Å (ε 49,400).

Alternatively, a hot mixture of 2-iodo-5 : 6-benzoquinoline ethiodide (1·15 g.), 2-methylbenzoxazole ethiodide, ethanol (10 c.c.), and triethylamine was boiled for 3 min. The solid was filtered off hot and washed with hot ethanol (2 × 1 c.c.); it consisted of unchanged iodo-compound, together with green crystals. The filtrate and washings slowly crystallised, giving a 13% yield of (washed) dye. After two recrystallisations of this from methanol (75 c.c. per g.), the first being with charcoal, the yield was 3%. The m. p. and mixed m. p. were those of the sample prepared by the first method, and the absorption maxima were identical (Found: C, 59·05; H, 4·95%). A solution of the washed residue (0·06 g.) from the original mother-liquor, in methanol (100 c.c.), was filtered hot and concentrated to 33 c.c., these being the conditions for recrystallising bis-2-(1-ethyl-5 : 6-benzoquinoline)methincyanine iodide, m. p. 310° (decomp.).[59] Green crystals (0·02 g.) separated, which remained unmelted at 302° (Found: C, 67·3; H, 4·9. Calc. for $C_{31}H_{27}N_2I$: C, 67·1; H, 4·9%). Methanolic solutions of the two dyes gave the same absorption maxima.

[2-(1-*Ethyl*-5 : 6-*benzoquinoline*)][2-(3-*ethylbenzoxazole*)]*phenylmethincyanine Iodide.*—2-Benzylbenzoxazole (0·62 g.) and ethyl toluene-*p*-sulphonate were heated at 155—165° for 4 hr. The resulting gum was dissolved in hot ethanol (8 c.c.), 2-iodo-5 : 6-benzoquinoline ethiodide was added, then triethylamine, and the mixture was boiled for 2 min. Hot filtration removed unchanged iodo-compound, which was washed with hot ethanol (2 c.c.). The filtrate and washings were treated with ether (100 c.c.), and the precipitated tar was washed with ether. Its solution in hot methanol (2 c.c.) was treated with potassium iodide (4 mols.) in water (25 c.c.). The washed solid (56% yield) was dissolved in chloroform, containing 1% of ethanol, and washed with this solvent on a column of alumina. A little yellow impurity was removed, the red dye was then collected (31% yield), and a yellow residue remained in the column. The dye was boiled in hot ethanol (20 c.c.) with charcoal, and the filtrate was treated hot with aqueous potassium iodide. The tar solidified when ground with ice and was dried (9% yield). After two crystallisations of this material from ethanol, with charcoal in the first, the red crystals (2%) had m. p. about 183° (decomp.), with shrinking from 150° (Found: C, 64·85; H, 5·1. $C_{31}H_{27}ON_2I$ requires C, 65·25; H, 4·75%). The *dye* was inert towards a chlorobromide and a bromoiodide emulsion.

[2-(3-*Ethylbenzoxazole*)][1-(2-*ethylisoquinoline*)]*methincyanine Iodide.*—2-Methylbenzoxazole ethotoluene-*p*-sulphonate (0·83 g.), 1-iodo*iso*quinoline ethiodide, ethanol (8 c.c.), and triethylamine were boiled for 15 min. Potassium iodide (4 mols.) in hot water (16 c.c.) was added. The washed, red *dye* (46%) on recrystallisation from ethanol (20 c.c. per g.) was obtained in 37% yield and had m. p. 228° (decomp.) (Found: C, 56·85; H, 5·1. $C_{31}H_{31}ON_2I$ requires C, 56·75; H, 4·75%).

[2-(3-*Ethylbenzoxazole*)][1-(2-*ethylisoquinoline*)]*phenylmethincyanine Iodide.*—To the quaternary salt from 2-benzylbenzoxazole (0·50 g.) and ethyl toluene-*p*-sulphonate were added 1-iodo-*iso*quinoline ethiodide, ethanol (7 c.c.), and triethylamine, and the mixture was boiled for 3 min. Potassium iodide (4 mols.) in hot water (32 c.c.) was added. The tar was washed with water and then with ether. It separated from hot ethanol (5 c.c.) in 27% yield [12% after two recrystallisations from water (100 c.c. per g.)]. The vermilion crystals had m. p. about 180° (decomp. from

[59] Hamer and Kelly, *J.*, 1931, 777.

<100°) (Found: C, 60·0; H, 5·0; I, 23·8. $C_{27}H_{25}ON_2I,H_2O$ requires C, 60·2; H, 5·05; I, 23·6%). The *dye* slightly desensitised a bromoiodide emulsion.

[2-(3-*Ethylbenzoxazole*)][4-(1-*ethylquinoline*)]*phenylmethincyanine Iodide*.—To the salt from 2-benzylbenzoxazole (1·08 g.) and ethyl toluene-*p*-sulphonate were added 4-iodoquinoline ethiodide, ethanol (10 c.c.), and triethylamine and the mixture was boiled for 3 min. A hot solution of potassium iodide precipitated the dye *iodide* as tar, which was washed with water, and dissolved in acetone (8 c.c.), whence it crystallised (16% yield) [4% after 3 recrystallisations from ethanol (10 c.c. per g.)]. The maroon crystals had m. p. 224° (decomp.) with previous softening (Found: C, 61·2; H, 5·1. $C_{27}H_{25}ON_2I$ requires C, 62·3; H, 4·85%). The dye slightly desensitised a bromoiodide emulsion.

C, Styryl Dyes.

2-4′-*Diethylaminostyrylbenzothiazole Ethiodide* (XIV; R = H, R′ = Et).—A mixture of 2-methylbenzothiazole ethiodide (3·05 g., 1 mol.), *p*-diethylaminobenzaldehyde (1 mol.), and acetic anhydride (20 c.c.) was boiled for 20 min., then poured into a hot solution of potassium iodide (4 mols.) in water (200 c.c.). The washed product (4·28 g.) was extracted with ether (4·18 g. left; 90% yield). After two recrystallisations from methanol (25 c.c. per g.) and one from ethanol (20 c.c. per g.) (yields 83, 73, and 62%), the indigo-blue crystals had m. p. 225° (decomp.), after losing solvent below 100° (Found: C, 54·3; H, 5·65. $C_{21}H_{25}N_2IS$ requires C, 54·3; H, 5·45%). The *dye* sensitised a bromoiodide emulsion to 6500 Å, with maxima at 5700 and 6100 Å.

2-(4-*Dimethylamino-α-methylstyryl*)*benzothiazole Ethiodide* (XIV; R = R′ = Me).—A solution of 2-ethylbenzothiazole ethiodide (3·19 g.) and *p*-dimethylaminobenzaldehyde in acetic anhydride was similarly boiled and treated with aqueous potassium iodide. The product (3·56 g.) was washed with water and extracted with ether; the residue (3·07 g.; 68%) was thrice extracted with hot benzene (66% yield left), then recrystallised from ethanol (40 c.c. per g.). The dark blue *dye* (57%) had m. p. 197° (decomp.) (Found: C, 53·1; H, 5·35. $C_{20}H_{23}N_2IS$ requires C, 53·3; H, 5·15%). Towards a chlorobromide emulsion there was weak sensitisation to 6300 Å, with maxima at 5300 and 5700 Å.

The *base* (0·36 g., 12%), which had been extracted by ether, was dissolved in hot benzene (10 c.c. per g.), and the solution treated with light petroleum (b. p. 60—80°; 10 c.c. per g.). After a second recrystallisation from acetic anhydride (17 c.c. per g.) (6% yield), the yellow crystals had m. p. 160° [Found: C, 73·2; H, 6·3; N, 9·5; S, 10·8%; *M* (Rast), 278. $C_{19}H_{18}N_2S$ requires C, 73·45; H, 6·15; N, 9·5; S, 10·9%; *M*, 294]. The base was thus 3-*ethyl*-2-[2-(4-*imino*cyclo*hexa*-2:5-*dienylidene*)-1-*methylethylidene*]*benzothiazoline* (XVI; R′ = H). The absorption maximum of a methyl-alcoholic solution was at 3840 Å (ε 15,400). The base produced slight desensitisation of a chlorobromide and a bromoiodide emulsion and was inert towards a pure chloride emulsion.

2-(4-*Diethylamino-α-methylstyryl*)*benzothiazole Ethiodide* (XIV; R = Me, R′ = Et).—A solution of 2-ethylbenzothiazole ethiodide (3·19 g., 1 mol.) and *p*-diethylaminobenzaldehyde in acetic anhydride (20 c.c.) was boiled for 30 min., then poured into water (100 c.c.). After cooling, the solid was filtered off and washed with water (0·74 g. obtained). By treatment of the filtrate with potassium iodide solution, a further 2·72 g. were obtained.

Recrystallisation of the second crop from water (20 c.c.; charcoal) gave inhomogeneous crystals. These were ground with cold water and left a terracotta residue (0·30 g.). Concentration of the filtrate to about 8 c.c. gave buff crystals (1·24 g.). By repeated extraction of the charcoal with methanol, concentration (to 5 c.c.), and treatment with ether, a further yield (0·14 g.) of terracotta solid resulted. The required dye (0·30 + 0·14 = 0·44 g.) (9% yield) recrystallised from ethanol (5 c.c.) (7% yield). It was boiled with benzene (2 × 10 c.c.), and the residue recrystallised from ethanol (4 c.c.) (6% yield). The red *product* had m. p. 192° (decomp.) (Found: C, 55·15; H, 5·95. $C_{23}H_{27}N_2IS$ requires C, 55·2; H, 5·7%). Sensitisation of a chlorobromide emulsion was from 4800 to 6100 Å with an indistinct maximum. The crystals (1·24 g.) from the aqueous extract were dissolved in hot water (20 c.c.), and the orange solution was treated with ammonia. The washed crystals (0·90 g.) made a further 19% yield of the dye, which was recrystallised from ethanol (10 c.c.) (a 12% yield) and had the same m. p. and mixed m. p. as the analytically pure dye (total yield 18%).

The original first crop (0·74 g.) was twice extracted with benzene (2 × 20 c.c.). The residue was dissolved in hot methanol, and this extract taken to small volume and treated with ether. The resultant dye (0·08 g.) was twice recrystallised from methanol (37 c.c. and 75 c.c. per g., respectively) (0·02 g. obtained) (Found: C, 52·45; H, 6·05. Calc. for $C_{21}H_{25}N_2IS,H_2O$: C,

52·25; H, 5·65%. The dark blue crystals had m. p. 225° (decomp.). This m. p. and the mixed m. p. were the same as that of 2-4′-diethylaminostyrylbenzothiazole ethiodide; identity was confirmed, since they had the same absorption maximum.

The preceding benzene extract gave a base (0·61 g., 19%). This was dissolved in hot benzene (3 c.c.), treated with light petroleum (b. p. 60—80°; 3 c.c.), decanted from some dark oil, and treated with more benzene and light petroleum (3 c.c. of each), yielding yellow crystals (11%). After two recrystallisations from ethanol (55 c.c. per g.) (7% yield), the m. p. was 137° (Found: C, 74·4; H, 6·95; N, 8·8; S, 9·65. $C_{29}H_{32}N_2S$ requires C, 74·45; H, 6·85; N, 8·7; S, 9·95%). The base was believed to be *3-ethyl*-2-[2-(4-*ethyliminocyclohexa*-2 : 5-*dienylidene*)-1-*methylethylidene*]*benzothiazoline* (XVI; R′ = Et). Its methanolic solution had its absorption maximum at 3930 Å (ε 13,600). It was inert towards a chlorobromide, a bromoiodide, and a pure chloride emulsion.

2-(4-*Dimethylamino*-α-*phenylstyryl*)*benzothiazole Ethiodide* (XIV; R = Ph, R′ = Me).—2-Benzylbenzothiazole ethiodide (0·76 g.), *p*-dimethylaminobenzaldehyde, and acetic anhydride (10 c.c.) were boiled for 30 min. The product was precipitated by ether, washed with water, and boiled with benzene (3 × 25 c.c.). The residual dye (63%) recrystallised from acetic acid (10 c.c. per g.) (56% yield). When the red crystals were heated, solvent was eliminated about 120° and there was shrinking; the m. p., about 180° (decomp.), depended on the rate of heating (Found: C, 58·65; H, 4·8. $C_{25}H_{25}N_2IS$ requires C, 58·55; H, 4·9%). The *dye* weakly sensitised a chlorobromide emulsion from 4800 to 6300 Å, with a maximum at 5800 Å.

2-(4-*Dimethylamino*-α-p-*nitrophenylstyryl*)*benzothiazole Ethiodide* (XIV; R = *p*-$C_6H_4{\cdot}NO_2$, R′ = Et).—2-*p*-Nitrobenzylbenzothiazole ethiodide (0·85 g.), *p*-dimethylaminobenzaldehyde, and acetic anhydride (10 c.c.) were boiled for 20 min., and added to potassium iodide (4 mols.) in water (100 c.c.). The washed solid (0·93 g.) was extracted with ether (61% yield of residue). It was recrystallised from methanol (10 c.c. per g.) (40% yield), boiled with benzene (2 × 45 c.c. per g.) (36% yield of residue), and recrystallised from methanol (26% yield) (Found: C, 53·45; H, 4·4. $C_{25}H_{24}O_2N_2IS$ requires C, 53·8; H, 4·35%). The terracotta *salt* had m. p. 203° (decomp.). It strongly desensitised a chlorobromide and a bromoiodide photographic emulsion.

The *base* (0·24 g., 30% yield), which had been extracted by ether, was dissolved in hot benzene (5 c.c.), and the solution treated with light petroleum (b. p. 60—80°; 5 c.c.) (15% yield). After recrystallisation from acetic anhydride (40 c.c. per g.), the yellow crystals (11% yield) had m. p. 220°. The m. p. was unchanged after another recrystallisation from acetic anhydride [Found: C, 68·35; H, 4·85; N, 10·45; S, 7·8%; *M* (Rast), 318·6. $C_{23}H_{19}O_2N_2S$ requires C, 68·8; H, 4·75; N, 10·45; S, 8·0%; *M*, 401·5]. The analysis indicates the structure *3-ethyl*-2-(2-4′-*iminocyclohexa*-2′ : 5′-*dienylidene*-1-p-*nitrophenylethylidene*)*benzothiazoline* (XVII). The absorption maximum of a methanolic solution was at 4040 Å (ε 37,900). The base was photographically inert when tested in a chlorobromide and in a bromoiodide emulsion.

2-(4-*Dimethylamino*-α-*ethoxycarbonylstyryl*)*benzothiazole Ethiodide* (XIV; R = CO_2Et, R′ = Me).—A solution of 2-ethoxycarbonylmethylbenzothiazole ethiodide (1·89 g., 1 mol.), *p*-dimethylaminobenzaldehyde (1 mol.), and triethylamine (1·2 mols.) in ethanol (15 c.c.) was boiled for 5 hr. and filtered hot (no residue). The dye crystallised on cooling and more was obtained by concentration (total 51%). It was boiled with ethanol (20 c.c. per g.; charcoal), and the filtrate was concentrated to 7 c.c. and allowed to crystallise. A further similar recrystallisation, followed by simple recrystallisation from ethanol (7 c.c. per g.), afforded a 24% yield. The orange crystals had m. p. 199° (decomp.) (Found: C, 52·2; H, 5·15. $C_{23}H_{25}O_2N_2IS$ requires C, 51·95; H, 4·95%). The *dye* sensitised a chlorobromide emulsion very weakly to 5600 Å with the maximum at 5250 Å.

2-(α-2′-*Benzothiazolyl*-4-*dimethylaminostyryl*)*benzothiazole Ethiodide* (XIV; R = 2-benzothiazolyl, R′ = Me).—A solution of dibenzothiazolylmethane ethiodide (1·46 g.) and *p*-dimethylaminobenzaldehyde in acetic anhydride (20 c.c.) was boiled for 10 min. The washed dye (84% yield) was recrystallised from methanol (38 c.c. per g.) (74% yield), then from acetic acid (47 c.c. per g.) (57%) and from methanol (54 c.c. per g.) (43%). The red crystals darkened about 100° and had m. p. 210° (decomp.) (Found: C, 54·55; H, 4·6. $C_{24}H_{24}N_2IS_3$ requires C, 54·85; H, 4·25%). On a chlorobromide emulsion the *dye* conferred weak sensitising to 5600 Å, tailing to 6000 Å, with the maximum at 5200 Å.

2-4′-*Dimethylaminostyrylbenzoxazole Ethiodide* (XV; R = H, R′ = Me).—To a hot solution of 2-methylbenzoxazole ethotoluene-*p*-sulphonate (1·67 g., 1 mol.) and *p*-dimethylaminobenzaldehyde (1 mol.) in ethanol (6 c.c.), triethylamine (0·12 mol.) was added, and the solution was boiled for 3 hr. Ether (60 c.c.) precipitated a red tar, which crystallised. Its solution in hot

methanol (5 c.c.) was treated with potassium iodide (4 mols.) in hot water (50 c.c.). The water-washed product (42%) was recrystallised from ethanol (50 c.c. per g.). The red crystals (30%) had m. p. 251° (decomp.) (Found: C, 54·3; H, 5·15. $C_{19}H_{21}ON_2I$ requires C, 54·25; H, 5·05%). The *dye* sensitised a bromoiodide emulsion weakly up to 6000 Å.

2-(4-*Dimethylamino-α-methylstyryl*)*benzoxazole Ethiodide* (XV; R = R′ = Me).—A solution of 2-ethylbenzoxazole ethiodide (1·52 g.) and *p*-dimethylaminobenzaldehyde in acetic anhydride (10 c.c.) was boiled for 5 min. The washed crystals (74%) were thrice extracted with hot benzene (total: 20 c.c.) (71% yield left). After recrystallisation from methanol (20 c.c. per g.) the bright red crystals (57%) had m. p. 210° (decomp.) (Found: C, 55·2; H, 5·4. $C_{20}H_{23}ON_2I$ requires C, 55·3; H, 5·35%). The *dye* weakly sensitised a chlorobromide emulsion to 5900 Å, with a maximum at 5400 Å.

2-(4-*Dimethylamino-α-phenylstyryl*)*benzoxazole Ethiodide* (XV; R = Ph, R′ = Me).—2-Benzylbenzoxazole (2·09 g.) and ethyl toluene-*p*-sulphonate were heated at 150—160° for 4 hr. The gum was dissolved in hot ethanol (10 c.c.), *p*-dimethylaminobenzaldehyde and triethylamine (0·12 g.) were added, and boiling was continued for 4 hr. The oil precipitated by ether was dissolved in hot methanol (8 c.c.) and added to a solution of potassium iodide (4 mols.) in hot water (40 c.c.). The washed product became brittle when dried (2·59 g. obtained). Much impurity was removed by treatment with acetone (7 c.c.). The 9% yield (0·44 g.) was reduced to 7% by recrystallisation from ethanol (30 c.c. per g.). The vermilion crystals had m. p. 223° (decomp.), with previous darkening (Found: C, 60·45; H, 5·2. $C_{25}H_{25}ON_2I$ requires C, 60·5; H, 5·35%). The *dye* sensitised a chlorobromide emulsion from 4900 to 5800 Å, with the maximum at 5500 Å.

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299. *Reactions of Organic Azides. Part V.* The Schmidt Reaction with Fluorenones. The Structure of the Intermediate in the Ketonic Schmidt Reaction.*

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The conversion of substituted fluorenones into phenanthridones, by means of the Schmidt reaction, is described. There is no simple correlation between the electronic character, or bulk, of a phenylene ring in a fluorenone, and its migratory aptitude. The data now available in the literature provide numerous exceptions to Smith's suggested rule [1,2,3] that, in the Schmidt reaction with an unsymmetrical ketone, the group having the larger bulk in the neighbourhood of the keto-carbon atom migrates preferentially.

It is shown that Smith's mechanism, which involves dehydration and re-hydration of reaction intermediates, is improbable. An intermediate containing a hydrogen-bonded ring is suggested.

The reaction of 2- and 3-substituted fluoren-9-ols with hydrazoic and sulphuric acids, to yield mixtures of the corresponding 2- and 7- or 3- and 6-substituted phenanthridines, is described in Part III.[4] The conversion, by the Schmidt reaction, of three monosubstituted fluorenones into pairs of isomeric phenanthridones is now reported.

Walls [5] was unable to isolate a pure product from the reaction of sodium azide with a solution of 2-methoxyfluorenone in sulphuric acid. By the addition of this fluorenone to a solution of hydrazoic acid in chloroform together with sulphuric acid, there has now been

* Part IV, *J.*, 1955, 1634.

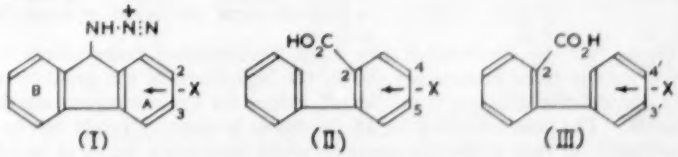
[1] Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 320.
[2] Smith and Ashby, *ibid.*, 1950, **72**, 2503.
[3] Smith and Horwitz, *ibid.*, p. 3718.
[4] Arcus and Coombs, *J.*, 1954, 4319.
[5] Walls, *J.*, 1935, 1405.

obtained a mixture of 2- and 7-methoxyphenanthridone in 36% yield. In order to separate the isomers, the mixture was converted by phosphorus oxychloride into the corresponding 9-chlorophenanthridines; the yield was almost quantitative, whence the ratio of 9-chloro-2-methoxy- to 9-chloro-7-methoxy-phenanthridine in the product must be nearly the same as that of the two methoxyphenanthridones in the original mixture. Fractional crystallisation yielded these chloromethoxyphenanthridines in substantially equal amounts, whence it is concluded that the ratio of 2- to 7-methoxyphenanthridone in the original reaction product was approximately 1 : 1.

It is stated [6] that 2-nitrophenanthridone is the sole product when a solution of 2-nitrofluorenone in sulphuric acid is allowed to react with a solution of hydrazoic acid in benzene. By the addition of sodium azide to a solution of 2-nitrofluorenone in sulphuric acid, Walls [5] obtained a mixture of nitrophenanthridones which on reduction gave a mixture of aminophenanthridones which he considered identical with that obtained from the Schmidt reaction with 2-aminofluorenone; the latter mixture was converted, *via* diazotisation, into a mixture of 2- and 7-hydroxyphenanthridones which he separated into its components. Repetition of the reaction by Walls's method gave a high yield of nitrophenanthridones. Fractional vacuum-sublimation of the product yielded a small quantity of a relatively volatile material approximating in m. p. to that of the 1 : 2-complex of 2- and 7-nitrophenanthridone reported by Nunn, Schofield, and Theobald,[7] and less volatile fractions consisting substantially of 2-nitrophenanthridone, which they yielded on one recrystallisation. From the weights of the fractions, 2- and 7-nitrophenanthridone are concluded to have been formed in the ratio 19 : 1.

The Schmidt reaction (as for the 2-isomer) with 3-nitrofluorenone gave a high yield of nitrophenanthridones, fractional vacuum-sublimation of which gave a least-volatile fraction yielding, on one recrystallisation, 3-nitrophenanthridone. By the use of authentic specimens of the isomers, a m. p.–composition curve was constructed, and by its use 3- and 6-nitrophenanthridone were found to have been formed in the ratio 69 : 31.

Mechanism of the Ketonic Schmidt Reaction.—Difference from the alcohol–olefin reaction. The migration ratios found for the phenanthridones formed from the three monosubstituted fluorenones, above, differ markedly from those relating to the similarly substituted phenanthridines derived from the corresponding fluoren-9-ols, respectively 32 : 68; 3 : 97; 6 : 94 (Part III [4]). The relative rates with which the substituted and unsubstituted rings migrate during the rearrangement of the protonated azide (whether derived from fluorenol or fluorenone) is directly given by the ratio of the yields of the corresponding phenanthridines (or phenanthridones). It is shown, qualitatively, in Part III,[4] that the ratios of the yields of isomeric phenanthridines are directly related to the capacities of the rings for electron-release at their point of attachment to $C_{(9)}$. It has been found possible to give this correlation a quantitative form, and to indicate the extent to which rates of migration of rings in the Schmidt reaction of the fluorenones are not correlated with electron-release.



In the rearrangement of the protonated azide (I), derived from a 2- (or 3-) substituted fluoren-9-ol, the rate of migration of ring A is dependent on the electron-availability at the point of attachment of A to $C_{(9)}$, and a measure of the " permanent " (*I* and *M*) part of this availability is given by the p*K* value of the corresponding 4- or 5-substituted diphenyl-2-carboxylic acid (II). Similarly, the electron-density at the point of attachment of B to $C_{(9)}$, which governs the rate of migration of ring B, is given by the p*K* value of the corresponding 3'- or 4'-substituted diphenyl-2-carboxylic acid (III).

[6] B.P. 333,173.

[7] Nunn, Schofield, and Theobald, *J.*, 1952, 2797.

On adapting the Hammett relation to a diphenyl system, and writing the rates of migration of A and B as k_A, k_B, and that of the unsubstituted phenylene ring [as in (I) with X = H] as k_H, and the pK values of the appropriate diphenyl-2-carboxylic acids as pK_A, pK_B, pK_H, we have :

$$\log (k_A/k_H) = r(pK_A - pK_H)$$

and

$$\log (k_B/k_H) = r(pK_B - pK_H)$$

where r is a constant, whence

$$\log (k_A/k_B) = r(pK_A - pK_B)$$

The ratio of the rate constants is the same as the ratio in which the products are formed, since the latter arise from a common precursor (I), whence :

$$\log \left[\frac{\% \text{ of product from migration of A}}{\% \text{ of product from migration of B}} \right] = r(pK_A - pK_B)$$

No dissociation constants are available for diphenyl-2-carboxylic acids except that for the unsubstituted acid.[8] However, Berliner and Blommers[9] have shown that the pK values for diphenyl-4-carboxylic acids, substituted in positions 3′ and 4′, and those for benzoic acids similarly substituted in the *meta*- and the *para*-position, are related by equation (1) having $a = 0{\cdot}37$:

$$pK_{X2} - pK_{Y2} = a(pK_{X1} - pK_{Y1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where X2 denotes diphenyl-4-carboxylic acid with substituent X, X1 denotes benzoic acid with the corresponding substituent, Y2 denotes diphenyl-4-carboxylic acid with substituent Y, and Y1 denotes benzoic acid with the corresponding substituent.

In order to estimate values for the substituted diphenyl-2-carboxylic acids, two assumptions have been made : that the strength of diphenyl-2-carboxylic acid is influenced by substituents in the 3′- and 4′-positions to the same extent as is that of the 4-carboxylic acid; and that substituents in positions 4 and 5 influence the strength of diphenyl-2-carboxylic acid to the same extent as they do that of benzoic acid. Then, taking Y = H in (1), and inserting $pK_{Y2} = pK$ (3·4597) for diphenyl-2-carboxylic acid,[8] and $pK_{Y1} = pK$ (4·2027) for benzoic acid,[10] pK_{X2} can be evaluated for 4-, 5-, 3′-, and 4′-substituted diphenyl-2-carboxylic acids by inserting the values of pK_{X1} appropriate to the corresponding *meta*- and *para*-substituted benzoic acids [10] and employing the values $a = 1{\cdot}00$ for 4- and 5-substituted and $a = 0{\cdot}37$ for 3′- and 4′-substituted diphenyl-2-carboxylic acids. By this means the following pK values have been estimated.

Diphenyl-2-carboxylic acid	4-NO_2	5-NO_2	4-Me	5-Me	4-MeO
pK	2·751	2·682	3·529	3·630	3·345
Diphenyl-2-carboxylic acid	3′-NO_2	4′-NO_2	3′-Me	4′-Me	4′-MeO
pK	3·197	3·172	3·485	3·523	3·559

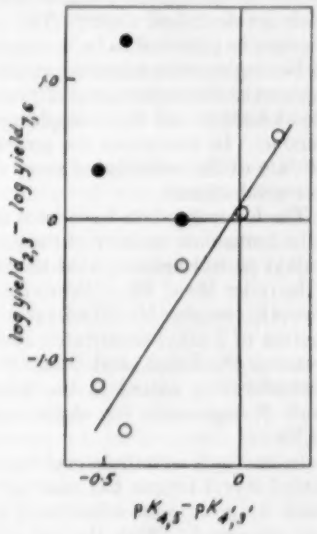
In the Figure, for the reactions of five 2- or 3-substituted fluoren-9-ols reported in Part III [4] and for the three fluorenones above, the logarithms of the product ratios have been plotted against the differences in the pK values for the corresponding diphenyl-2-carboxylic acids. The points relating to the fluorenols lie near a straight line to an extent which is considered, in view of the assumptions which have been made, to be adequate to establish a direct correlation between the rate of migration of a ring and the electron-density at its point of attachment to $C_{(9)}$. No such correlation is apparent for the points relating to the fluorenones.

The mechanism by which, it is considered, fluoren-9-ols react with hydrazoic and sulphuric acids is set out in Parts I,[11] III,[4] IV.[12] Essentially similar mechanisms are

[8] Dippy and Lewis, *J.*, 1937, 1426.
[9] Berliner and Blommers, *J. Amer. Chem. Soc.*, 1951, **73**, 2479.
[10] Dippy, *Chem. Rev.*, 1939, **25**, 151.
[11] Arcus and Mesley, *J.*, 1953, 178.
[12] Arcus and Lucken, *J.*, 1955, 1634.

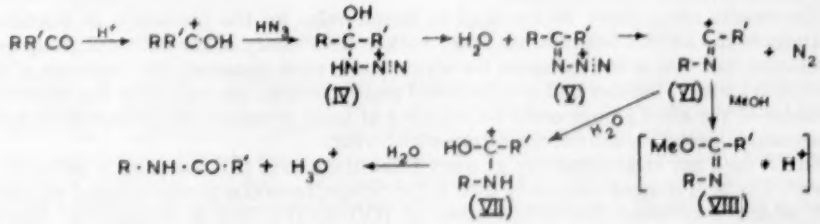
applicable to the reaction of 1 : 1-diarylethylenes with these reagents,[13] and the acid-catalysed decomposition of diarylazidomethanes [14] and of 1 : 1-diarylazidoethanes; [15] in each instance the respective authors have found that the migratory aptitude of a given group is directly related to its capacity for electron-release.

The results, reported above, on the Schmidt reaction with fluorenones add to the evidence [2,3,16] that the correlation between capacity for electron-release and migratory aptitude does not apply to the groups adjacent to the carbonyl group of a ketone which is undergoing the Schmidt reaction. It is concluded that there is a definite difference between the mechanism of the reaction of an alcohol or olefin with hydrazoic acid (in the presence of a strong acid), and that of a ketone with these reagents.



Relation of yields of isomeric phenanthridines, and phenanthridones, from the reaction of fluoren-9-ols (○), *and fluorenones* (●), *with hydrazoic and sulphuric acids, to values of* pK *of the corresponding diphenyl-2-carboxylic acids.*

The Structure of the Intermediate in the Ketonic Schmidt Reaction.—Smith [1,2,3] concluded from the available data that, in the Schmidt reaction with an unsymmetrical ketone, the group which has the larger bulk in the immediate neighbourhood of the keto-carbon atom usually migrates preferentially, and he proposed the following mechanism, which accommodates this finding :



The protonated azide (IV) loses water to give an oxime-like intermediate (V), which then undergoes a rearrangement analogous to the Beckmann rearrangement; (V) may be formed in either of two geometrically isomeric configurations, whence it is possible for the

[13] McEwen and Mehta, *J. Amer. Chem. Soc.*, 1952, **74**, 526.
[14] Tietz and McEwen, *ibid.*, 1955, **77**, 4007.
[15] Ege and Sherk, *ibid.*, 1953, **75**, 354.
[16] Westland and McEwen, *ibid.*, 1952, **74**, 6141.

isomer having the larger group *anti* to the N_2^+ group to be formed preferentially; rearrangement of this form leads to migration of the larger group. Hydration of the product from the last stage yields the protonated amide (VII).

An examination of the results of Schmidt reactions with unsymmetrical ketones, many reported since Smith's mechanism was proposed, shows that there are numerous exceptions to the rule that the group having the greater bulk in the vicinity of the carbonyl group migrates preferentially.

The evidence on electronic effects in the ketonic Schmidt reaction, referred to above, is derived from the reactions of *p*- and *pp'*-substituted benzophenones. The aryl groups of these ketones have essentially the same bulk in the neighbourhood of the carbonyl group, and this is substantially true of the two rings of the fluorenones, the Schmidt reactions of which are described above. The migratory aptitudes of rings in these compounds might therefore be expected to be unaffected by the presence of substituents. The aryl groups of the benzophenones migrated at about the same rate, except for *p*-methoxyphenyl, which migrated at twice the speed of phenyl in 4-methoxybenzophenone, but at nearly the same rate as 4-nitro- and 4-chloro-phenyl in 4-methoxy-4'-nitro- and 4-chloro-4'-methoxy-benzophenone. In fluorenone the presence of a 2-methoxy-group did not affect the migratory aptitude of the substituted ring, which was increased by a 3-nitro- and markedly by a 2-nitro-substituent.

The following data have been recorded concerning ketones which are not symmetrical in the immediate vicinity of the carbonyl group. Smith and Horwitz [3] found, for a series of alkyl phenyl ketones, that the relative extent of migration of the alkyl group increases in the order Me < Et < Pr^i < Bu^t (the course of the reaction with *tert.*-butyl ketones is, however, complex [17]). The substituted carbon atom migrates preferentially during the reaction of 2-alkyl-substituted *cyclo*pentanones and *cyclo*hexanones, also of 2-cyano*cyclo*hexanone.[18] Fusco and Rossi [19] have found the phenyl group to migrate to the preponderating extent in the Schmidt reactions of a series of ketones $C_6H_5{\cdot}CO{\cdot}CH_2X$, where X represents the electron-attracting substituents CN, $CO{\cdot}NH_2$, $CO{\cdot}NHPh$, NO_2, SO_2Ph.

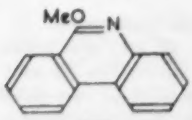
In methyl α-methylstyryl ketone the larger group migrates preferentially, and in methyl styryl ketone the smaller.[3] The reactions of a number of ketones $Ar{\cdot}CO{\cdot}Ph$, in which Ar is an *ortho*-substituted aryl group or an analogous polycyclic group, have been examined. With the following the larger group migrates preferentially: 2-nitro-, 2-phenyl-, 2 : 4 : 6-trimethyl-benzophenone; [20] 3-benzoyl-2 : 5-dimethylthiophen.[21] In the following the smaller group migrates preferentially: 2-methyl-, 2-chloro-, 2-bromo-benzophenone; [20] 1-benzoylnaphthalene; [21] 1-benzoylphenanthrene.[22] The reaction of *o*-aroylbenzoic acids has been shown to proceed *via* a cyclic cation the formation of which involves the intervention of the carboxyl group,[23] whence these compounds cannot be regarded as simple 2-substituted benzophenones.

The results cited above do not lead to simple rules for the prediction of migratory aptitudes in the ketonic Schmidt reaction; bulk in the vicinity of the carbonyl group may be a factor, but two of the instances for which this is most apparent, the reactions of the above alkyl phenyl ketones and ω-substituted acetophenones, are such that the migratory aptitudes of the alkyl groups could be regarded as being promoted by inductive electron-release and inhibited by inductive electron-withdrawal.

Smith does not state explicitly at what point the cation (VI) takes up a molecule of water. The acid reagent commonly used in the Schmidt reaction is concentrated sulphuric acid, which may effect the dehydration of (IV) to (V), but is unlikely to liberate water to convert (VI) into (VII), whence it is concluded that this last step would occur when the sulphuric acid solution is diluted with water at the end of the reaction. This

[17] Zook and Paviak, *J. Amer. Chem. Soc.*, 1955, **77**, 2501.
[18] Shechter and Kirk, *ibid.*, 1951, **73**, 3087.
[19] Fusco and Rossi, *Gazzetta*, 1951, **81**, 511.
[20] Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 431.
[21] Badger, Howard, and Simons, *J.*, 1952, 2849.
[22] Dice and Smith, *J. Org. Chem.*, 1949, **14**, 179.
[23] Arcus and Coombs, *J.*, 1953, 3698.

circumstance offers a means of testing the validity of the mechanism, for replacement of water by methanol as nucleophilic diluent would be expected to lead to the formation of the methoxy-compound (VIII). If a fluorenone is used, then a 9-methoxyphenanthridine (IX) is the expected product on Smith's mechanism.



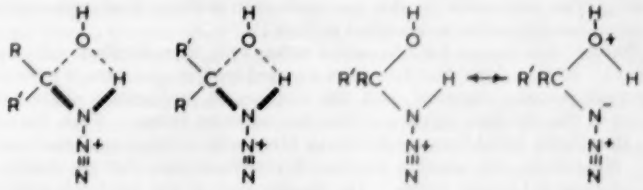
(IX)

The test was first made with 2-nitrofluorenone; part of the sulphuric acid solution from the Schmidt reaction was poured into dry methanol and part into ice and water: each gave a mixture of 2- and 7-nitrophenanthridone. The test was then carried out with fluorenone, which yields a single product, phenanthridone. It was originally intended to employ sulphuric acid containing sufficient free sulphur trioxide to combine with the water supposed to be eliminated as in (IV) ⟶ (V), but this reagent was found to sulphonate fluorenone completely. Reaction was therefore effected in 100% sulphuric acid; fluorenone dissolved in this acid, but, on dilution of the solution with water, 99·5% was recovered. The sulphuric acid solution from the Schmidt reaction was added to cold, dry methanol; phenanthridone was precipitated, and a pure specimen was obtained by recrystallisation from the non-hydroxylic solvent toluene.

There appears to be no probable mechanism whereby 9-methoxyphenanthridine, if it were formed during the above procedure, could become converted into phenanthridone. However, this compound has been prepared by the reaction of 9-chlorophenanthridine with methanolic sodium methoxide; a solution of 9-methoxyphenanthridine in methanolic sulphuric acid containing 1 mol. of water relative to the methoxy-compound gave no precipitate, and 94% of the 9-methoxyphenanthridine was recovered.

It is concluded that neither re-hydration of (VI), nor the formation of (V) by dehydration, takes place during the Schmidt reaction.

The following structure is proposed for the intermediate in the ketonic Schmidt reaction. Inspection of a model of the protonated azide (IV) shows that the hydrogen atom bonded to nitrogen closely approaches the hydroxylic oxygen atom when the molecule is in the conformations (X) and (XI), and it is suggested that a hydrogen bond is formed between the nitrogen and the oxygen atom, giving rise to a four-membered ring. The ring nitrogen



(X) (XI) (XII) (XIII)

is considered to possess a pyramidal configuration, whence two geometrically isomeric forms, spatially represented in (X) and (XI), are possible for the protonated azide. The structures which contribute to the hydrogen bond are shown in (XII) and (XIII).

The group which is *trans* to the N_2-group migrates when the latter separates; form (X) thus yields R′·CO·NHR, and form (XI) yields R·CO·NHR′. [Both (X) and (XI) possess an optical isomer, and each is representative of a racemic mixture; however, this is not relevant to the mechanism.]

The configuration of the $>N–N_2^+$ unit relative to the groups R and R′ would be expected to depend partly on the polar forces between these structures, and partly on the bulk of these groups in the neighbourhood of the unit.

2 : 7-*Dinitrophenanthridine*.—This compound has been synthesised by the following method: the Schmidt reaction with 2 : 7-dinitrofluorenone [5] gave 2 : 7-dinitrophenanthridone; this was converted into 9-chloro-2 : 7-dinitrophenanthridine and thence, *via* the toluene-*p*-sulphonhydrazide, into 2 : 7-dinitrophenanthridine.

Experimental

M. p.s are corrected.

The preparation of 2-methoxy-, 2-nitro-, and 3-nitro-fluorenone has been described.[24]

The Schmidt Reaction.—2-Methoxyfluorenone. Sulphuric acid (98%; 22 ml.) was added dropwise to a cooled and stirred suspension of sodium azide (7·3 g.) in chloroform (75 ml.). After 10 min., the temperature was raised to 25° and 2-methoxyfluorenone (15·6 g.) was added in small portions during 2 hr. After a further hour, water was added and the whole was shaken; there separated a brown solid (12·4 g.), m. p. 195—215°, which was collected, dried, and sublimed at 200°/0·001 mm. Eight fractions of a cream-coloured microcrystalline solid (5·95 g.) were obtained, all of which melted within the range 229—241°; the non-volatile black residue (4·0 g.) contained nitrogen and sulphur. The last fraction (0·50 g.), m. p. 237—241°, on recrystallisation from pyridine gave needles of 2- and 7-methoxyphenanthridone (0·35 g.), m. p. 239—242° (Found: C, 74·4; H, 4·95; N, 6·4. Calc. for $C_{14}H_{11}O_2N$: C, 74·65; H, 4·9; N, 6·2%). The rest of the sublimate was heated under reflux for 4½ hr. with phosphorus oxychloride (25 ml.), and the solution was cooled and poured on ice; the precipitate (5·55 g.), m. p. 104—112°, was collected, dried, and fractionally crystallised from light petroleum (b. p. 60—80°, 500 ml.). The first crop (2·4 g.), m. p. 133—135°, yielded on recrystallisation 9-chloro-2-methoxyphenanthridine (1·7 g.), m. p. 136—137°. Further crops (2·6 g., m. p.s in the range 94—104°) gave on recrystallisation 9-chloro-7-methoxyphenanthridine (1·95 g.), m. p. 101—103°, raised to 104° by a second recrystallisation. Walls [5] records m. p. 137·5° for 9-chloro-2- and m. p. 107° for 9-chloro-7-methoxyphenanthridine.

2-Nitrofluorenone. To a stirred solution of 2-nitrofluorenone (5·0 g.) in sulphuric acid (28 ml.) at 0°, sodium azide (2·8 g.) was added during 1 hr. After a further 30 min. the solution was poured on ice, and the yellow solid which separated (5·3 g.), m. p. 326—336°, was collected, washed, and dried. This material (500 mg.) was sublimed at 210°/0·5 mm. in 11 fractions: the first four (total 30 mg.) melted at 282—308° and on crystallisation from pyridine formed a microcrystalline powder (20 mg.) having m. p. 298—303°; the last 7 fractions (total, 390 mg.), m. p. 335—342°, on recrystallisation from pyridine yielded 2-nitrophenanthridone (230 mg.), m. p. 360°. Nunn, Schofield, and Theobald [7] record m. p. 357—358° for 2-nitrophenanthridone and m. p. 286—287° for the 1 : 2 complex of 2- and 7-nitrophenanthridone.

Recrystallisation from pyridine (700 ml.) of the crude material (25 g.; m. p. 325—335°) from a second experiment, with 25 g. of 2-nitrofluorenone, yielded 2-nitrophenanthridone (15 g.), m. p. 358—359°. The conversion of this specimen into 9-chloro-2-nitrophenanthridine, and thence into 2-nitrophenanthridine is described in Part III.[4]

Methanol (700 ml.) was heated for 4 hr. under reflux with, then distilled from, freshly ignited quicklime (140 g.); 50 ml. of the distillate were warmed with magnesium (3 g.) and a crystal of iodine; a vigorous reaction occurred, and the solution of magnesium methoxide was then added to the rest of the distillate which was then heated under reflux. Next, the methanol was distilled into a thoroughly dried three-necked flask fitted with a dropping funnel and a mercury-sealed stirrer. Meanwhile, the reaction between 2-nitrofluorenone (5·0 g.), sodium azide, and sulphuric acid was carried out as above. The greater part of the sulphuric acid solution was then added dropwise to the stirred methanol, which was cooled in ice and salt. The precipitate was collected, washed with absolute ethanol, then with light petroleum, and dried in an oven; it (4·4 g.) had m. p. 325—329°. The rest of the sulphuric acid solution was poured on ice and yielded a product having m. p. 321—325°, and m. p. 322—326° when mixed with the product from methanol-dilution. The slightly higher m. p. of the latter product is attributed to the extraction of impurities by the methanol.

3-Nitrofluorenone. (M. p.s in this section are uncorrected.) This compound (5·0 g.) was subjected to the Schmidt reaction by the procedure described for the 2-isomer. Of the product (5·2 g.), m. p. about 340°, 4·7 g. were sublimed at 220°/0·1 mm. in 22 fractions, all yellow powders; the residue was a black amorphous solid. Fraction 4 (15 mg.), m. p. 333—340°, was analysed (Found: C, 64·7; H, 3·55. Calc. for $C_{13}H_8O_3N_2$: C, 65·0; H, 3·35%). The highest-melting fraction (56 mg.), m. p. 365—367°, on crystallisation from pyridine yielded 3-nitrophenanthridone (38 mg.), cream-coloured needles, m. p. 372—374° alone and when mixed with the authentic compound, having m. p. 372°, prepared by the nitration of phenanthridone according to Moore and Huntress.[25] The first, and lowest-melting, fraction (83 mg.), m. p. 332—334°, on crystallisation from pyridine yielded yellow needles (41 mg.), m. p. 333—335°, of (below) the

[24] Arcus and Coombs, *J.*, 1954, 3977.
[25] Moore and Huntress, *J. Amer. Chem. Soc.*, 1927, **49**, 1332.

1 : 1 eutectic mixture of 3- and 6-nitrophenanthridone. By the use of authentic specimens of 3- and 6-nitrophenanthridone (the latter, m. p. 368°, was prepared as described in Part III [4]), a m. p.–composition curve was constructed by the method previously given; [4] the electrically

6-Nitrophenanthridone (%)	20	40	50	60	80
M. p. (first determ.)	360°	342°	337°	344°	355°
(second determ).	358°	339°	335°	345°	357°

heated m. p. apparatus was preheated to 320°. The facts that the m. p. of the first fraction is very nearly that of the eutectic, and that 68% of 3-nitrophenanthridone was isolated from the highest-melting fraction, demonstrate all the fractions to contain 50% or more of the 3-isomer. This was verified by determination of m. p.s of mixtures of an intermediate fraction with 3- and with 6-nitrophenanthridone. The compositions of the fractions were read off from the curve, whence the sublimate was found to contain 2·43 g. of 3- and 1·10 g. of 6-nitrophenanthridone.

2 : 7-*Dinitrofluorenone*. 2 : 7-Dinitrofluorene [26] (45 g.), glacial acetic acid (1·5 l.), and chromium trioxide (36 g.) were heated under reflux for 75 min., and allowed to cool. The solid which separated was collected, washed with water, and crystallised from pyridine (700 ml.); it yielded yellow needles of 2 : 7-dinitrofluorenone (30 g.), m. p. 295—296° (Schultz [27] records m. p. 291—292°, but gives no details of the preparation). Reaction of this compound (15·0 g.) with sulphuric acid and sodium azide according to Walls [5] gave 2 : 7-dinitrophenanthridone (15·6 g.), m. p. >380°, which was converted into 9-chloro-2 : 7-dinitrophenanthridine (10·5 g.), m. p. 225—227°, by the method of Albert,[28] who records m. p. 225°.

A solution of this compound (10·5 g.) and toluene-*p*-sulphonhydrazide (10·0 g.) in chloroform (850 ml.) was boiled under reflux for 60 hr. in the course of 5 days, and the crystalline precipitate (14·8 g.), m. p. 200° (decomp.), was collected. In 0·5N-sodium hydroxide (1·5 l.) it gave an almost black suspension which when stirred at 80° evolved nitrogen. After 80 min. the suspension was cooled, and the solid was collected and extracted with boiling 5N-hydrochloric acid (200 ml.). The extracts were poured into an excess of 5N-sodium hydroxide; there separated an orange solid (3·0 g.), m. p. 290—300°, which was sublimed *in vacuo*; the sublimate, on crystallisation from chlorobenzene, yielded 2 : 7-*dinitrophenanthridine*, yellow needles, m. p. 302° (Found : C, 58·2; H, 2·6; N, 15·3. $C_{13}H_7O_4N_3$ requires C, 58·0; H, 2·6; N, 15·6%).

Fluorenone : methanol dilution. Fluorenone (2·0 g.) was dissolved in oleum (containing 83·4% of SO_3, *i.e.*, 9·5% of free SO_3; 15 ml.), and the solution was poured on ice; a clear aqueous solution resulted. Sulphuric acid (100%) was prepared by the following method, based on Brand's observations; [29] to acid somewhat below this strength, oleum (20% of free SO_3) was added from a burette until a permanent fuming was obtained; sulphuric acid (95%) was similarly added until fuming just ceased. The acid so prepared had $d_{15\cdot6}^{15\cdot6}$ 1·8393; Fairlie [30] records $d_{15\cdot6}^{15\cdot6}$ 1·8391 for 100·0% sulphuric acid.

Fluorenone (2·042 g.) was stirred with ice-cold sulphuric acid (100%; 15 ml.) for 1 hr. The resulting solution was poured on ice; the solid which separated was collected in a sintered glass crucible, washed with water, and dried, in air at 38°, then *in vacuo*, to constant weight (2·029 g.).

To a stirred solution of fluorenone [distilled, and recrystallised from benzene–light petroleum (b. p. 40—60°); m. p. 83°; 4·5 g.] in sulphuric acid (100%; 60 g.), in a flask protected by a calcium chloride tube and cooled in ice, sodium azide (3·25 g.) was added from a closed hopper during 1½ hr. Stirring was continued for a further hour. The solution was then added dropwise to chilled dry methanol (650 ml.) prepared and used as described for 2-nitrofluorenone. A brown solid separated; it was collected, washed with dry methanol and with light petroleum (b. p. 40—60°), and dried *in vacuo*; the greater part was soluble in hot toluene (dried over sodium; 340 ml. of boiling toluene dissolve 1·0 g. of phenanthridone) from which it was recrystallised. The experiment was repeated. There were obtained :

	Original product	1st recrystalln.		4th recrystalln.	
	wt.	m. p.	m. p.	mixed m. p.*	m. p.	mixed m. p. *
(i)	3·2 g.	282·5—290·5°	291—293·5°	293·5—294°	293·5—294°	294—294·5°
(ii)	2·8 g.	281·5—287·5°	291—292·5°	292·5—294·5°	293·5—294·5°	293·5—294·5°

* With a standard specimen of phenanthridone having m. p. 293·5—294·5°.

[26] Courtot, *Ann. Chim.* (*France*), 1930, **14**, 83.
[27] Schultz, *Annalen*, 1880, **203**, 104.
[28] Albert, *J.*, 1948, 1284.
[29] Brand, *J.*, 1946, 585.
[30] Fairlie, "Sulphuric Acid Manufacture," Reinhold Publ. Corp., New York, 1936, p. 611.

Phenanthridone (2·0 g.) and phosphorus oxychloride (10 ml.) were boiled under reflux for 9 hr. The solution was poured into stirred ice–water; stirring was continued for 1 hr. and the solid product was collected, dried *in vacuo*, and extracted with ether (60 ml.). The extract yielded 9-chlorophenanthridine (1·8 g.), m. p. 115—116°, and m. p. 118·5° after repeated recrystallisation from ether (Graebe and Wander [21] record m. p. 116·5°). Preparations on a larger scale gave smaller percentage yields.

Sodium (1·54 g.) was allowed to react with dry methanol (61 ml.), and to the cooled solution was added 9-chlorophenanthridine (13·0 g.); the whole was boiled under reflux for 1 hr. and poured into ice–water. The solid which separated was collected, washed, and dried *in vacuo*; the greater part of the product dissolved in hot light petroleum (b. p. 60—80°), whence separated *9-methoxyphenanthridine* (11·0 g., m. p. 42—48°) which, after further recrystallisation, formed needles, m. p. 54·5° (Found: C, 80·25; H, 5·35; N, 6·6. $C_{14}H_{11}ON$ requires C, 80·35; H, 5·3; N, 6·7%).

A solution of 9-methoxyphenanthridine (5·190 g.) in dry methanol (95 ml.) was added to a solution, cooled to −8°, prepared from dry methanol (600 ml.), sulphuric acid (100%, 30 ml.), and a 5N-solution of water in methanol (5·0 ml.). After 15 min., during which it remained clear, the solution was poured into a stirred mixture of sodium carbonate (127 g.) and ice (1½ kg.). After 1 hr., water was added and the whole was extracted with light petroleum (b. p. 40—60°; 3 × 150 ml.). The extract was washed with aqueous sodium carbonate, and with water, and dried (Na_2SO_4), and the solvent distilled. The 9-methoxyphenanthridine so recovered was dried *in vacuo* over sulphuric acid and paraffin wax to constant weight (4·881 g.); it had m. p. 51° and, after three recrystallisations from light petroleum (b. p. 60—80°), m. p. 54°, mixed m. p. 54·5°.

Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited for grants.

Battersea Polytechnic, London, S.W.11. [*Received, October 4th*, 1955.]

[21] Graebe and Wander, *Annalen*, 1893, **276**, 250.

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300. *The Production of Active Solids by Thermal Decomposition. Part VIII.* Calcination of Calcium Hydroxide.*

By D. R. Glasson.

The specific surface, S, of the product obtained by calcining calcium hydroxide (*a*) for a fixed time of 5 hours at different temperatures, (*b*) for various times at each of a number of fixed temperatures, has been measured by sorption of nitrogen (and occasionally of oxygen) at −183°. *X*-Ray powder photographs of certain calcined samples have been taken. At lower calcination temperatures, notably 350—500° *in vacuo*, the decomposition of the calcium hydroxide results in a several-fold increase in S; this is ascribed to the newly formed calcium oxide being activated when (according to the *X*-ray data) it recrystallises from a pseudo-lattice of calcium hydroxide to very small individual crystals having a more stable lattice structure. The specific surface ultimately decreases on further calcination because of sintering of the calcium oxide, which is enhanced by an increase in temperature. Recrystallisation of the calcium oxide is apparently inhibited by traces of chemisorbed carbon dioxide and water, particularly below 500° in air.

Thermal decomposition of calcium hydroxide produces calcium oxide varying considerably in surface activity according to the temperature and time of calcination: the decomposition thus proves suitable for demonstrating changes in physical structure postulated in Part I [1] for the products of reactions of type: Solid A ⟶ Solid B + Gas. The specific surface areas and volatile-matter contents of the calcined samples were determined, and *X*-ray powder photographs of certain samples were taken. The results show that the calcium

* Part VII, *J.*, 1955, 3804.

[1] Gregg, *J.*, 1953, 3940.

oxide, *i.e.*, solid B, is activated after its production from the calcium hydroxide, *i.e.*, solid A, probably through recrystallisation of a pseudo-lattice; the activated oxide sinters on further calcination.

Experimental

Materials.—The starting material was a batch of calcium hydroxide obtained from British Drug Houses, and contained small amounts of adsorbed water (1·10—1·13%) measurable by complete removal *in vacuo* below 200°. An additional weight loss of 24·43% occurred on calcination in air at 1000° on a thermal balance [3] corresponding to a composition of 99·5% of $Ca(OH)_2$ and 0·5% of $CaCO_3$ for the dried material. Its specific surface area was 4·9 and 5·2 $m.^2 g.^{-1}$, as measured by sorption of nitrogen and of oxygen respectively. Details of the nitrogen and oxygen used are given in Part II.[3]

Procedure.—Separate portions of the calcium hydroxide were calcined for 5 hr. at a succession of fixed temperatures either *in vacuo* on an electrical sorption balance [4] (at 350°, 450°, and 500°) or in air in an electrical furnace (at 450°, 500°, 600°, 700°, 800°, 900°, and 1000°). Further portions were calcined for varying periods *in vacuo* (at 200°, 250°, 300°, 350°, 400°, 450°, and 500°) and in air (at 450°).

To determine the specific surface, S, of the cooled samples, the sorption isotherms of nitrogen and of oxygen, both at −183° and up to a maximum pressure of 1 atm., were first determined gravimetrically by using the electrical sorption balance; [4] the lower part of the limb of the balance was surrounded by a liquid-oxygen bath, the temperature of which (read by an oxygen vapour-pressure thermometer) remained constant within ±0·2°; at least 1 hr. was allowed for the sample to attain this temperature. The oxygen isotherms, which extended to a relative pressure, p/p_0, near unity, were of type II (B.E.T. classifications [5]) with no hysteresis at $p/p_0 < 0{\cdot}3$; from these and the nitrogen isotherms, S could be calculated by the B.E.T. procedure [6] by use of values of 14·1 $Å^2$ and 17·0 $Å^2$ for the cross-sectional areas Am of oxygen and of nitrogen; this gave agreement within *ca.* 5% in the values of S obtained from both series of isotherms.

Results and Discussion

In Fig. 1*a* the specific surface, S, is plotted against the time of calcination for each of four temperatures of the "vacuum" experiments alongside the corresponding curves (Fig. 1*b*) for the percentage decomposition against time; S increases as the percentage decomposition increases, reaching a maximum when the decomposition is approximately complete (cf. A and A', B and B', C and C', D and D'); thereafter it slowly decreases with increasing time of calcination. The system thus provides a further example of the first type of active solid described in Part I,[1] and the increase in surface area therefore constitutes an activation ascribed to an increase in the number of micro-regions * in the decomposition product as compared with the initial substance; and the decrease in area to a sintering of the product.

The maximum (A, B, C, D) moves progressively to the left and downward as the calcination temperature is raised, the first movement denoting that the rate of decomposition (and therefore of activation) increases with rise in temperature, and the second that the product is more extensively sintered; however, the *rate* of sintering, as measured by the slopes of the "sintering branches" of the specific surface–time graphs, does not greatly increase with rise in temperature.

In Fig. 2*a* the specific surface, S, and in Fig. 2*b* the percentage decomposition, is plotted against the temperature for samples calcined for fixed times; S always shows a maximum (A, B, C) located at about the temperature where decomposition is just complete in the given time (A', B', C'). In accord with Part I,[1] the surface area at first increases with rise in temperature, since increasing proportions of calcium hydroxide are decomposed in a

* Crystallites having perfect or slightly imperfect lattices (cf. Part I, p. 3940).

[2] Gregg and Winsor, *Analyst*, 1945, **70**, 336.
[3] Gregg and Hill, *J.*, 1953, 3945.
[4] Gregg, *J.*, 1946, 561.
[5] Brunauer, Deming, Deming, and Teller, *J. Amer. Chem. Soc.*, 1940, **62**, 1723.
[6] Brunauer, Emmett, and Teller, *ibid.*, 1938, **60**, 309.

given time, but it decreases on further rise in temperature when the calcium oxide sinters more rapidly and for longer periods.

The plot of specific surface, S, against the percentage decomposition, m, in Fig. 3*a* reveals the interesting fact that, whilst S is approximately proportional to m for about the first 80% of the decomposition, yet S increases much more rapidly than m for the last 20%. The converse might have been expected in that the calcium oxide first formed has apparently had progressively longer in which to sinter, and a curve concave to the m axis would not be surprising. A similar anomaly was found during the decomposition of magnesium hydroxide [7] and may be similarly explained : the calcium oxide when first formed has a pseudo-lattice of calcium hydroxide, and recrystallises, but only at a limited

FIG. 1. *Calcium hydroxide samples calcined* in vacuo *at various temperatures.*

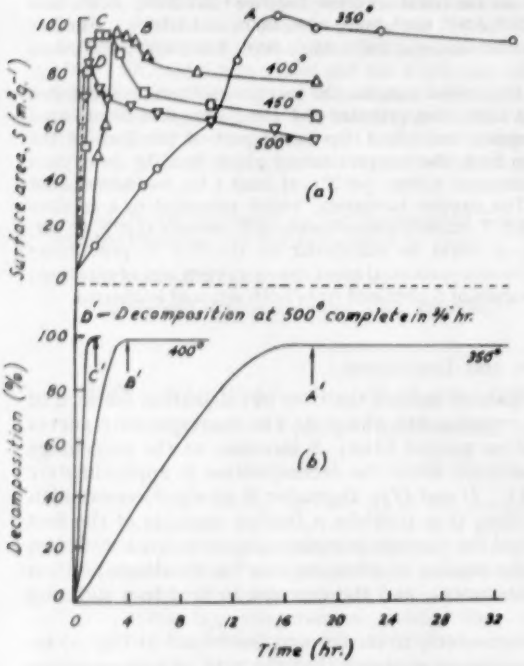
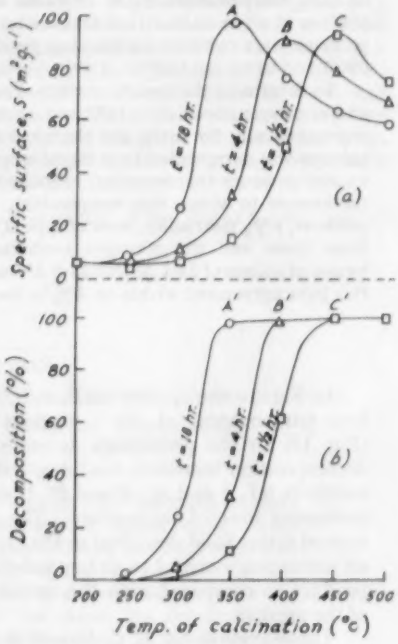


FIG. 2. *Samples calcined for periods t* in vacuo *at temperatures between 200° and 500°.*



rate, to true calcium oxide which subsequently sinters. Since the recrystallisation increases S, the time lag in the recrystallisation explains the fact that the production of new surface lags behind the decomposition.

The state of affairs is strikingly illustrated in Fig. 3*b*, which plots the specific surface, S', of the calcium oxide itself (S' has been calculated from S by subtracting the area of the calcium hydroxide, assumed to be proportional to the weight present). During the decomposition of the last 20% of the calcium hydroxide, S' increases, corresponding to the expected recrystallisation of the pseudo-lattice.

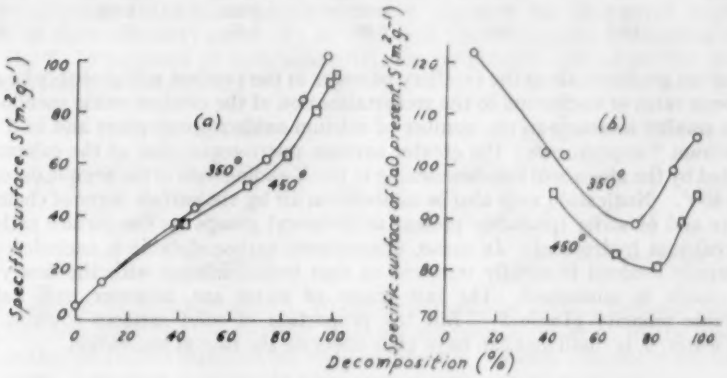
This explanation is supported by X-ray data : a sample calcined *in vacuo* at 450° for ½ hr. and having the composition (calculated from the percentage decomposition) $Ca(OH)_2$ 40% ; CaO, 60%, nevertheless showed the powder pattern corresponding to almost 100% $Ca(OH)_2$. (The X-radiograms of completely decomposed samples showed for various

[7] Gregg, Packer, and Wheatley, *J.*, 1955, **46**.

temperatures the weak and broadened lines to be expected for very small crystallites in random orientation, and thus qualitatively supported the specific-surface data.)

In Fig. 4, the specific surface, S, is plotted against the temperature for samples calcined for 5 hr. in air; S continuously decreases with increasing calcination temperature, so that as in the " vacuum " experiments, sintering of the calcium oxide is enhanced by increase in temperature. In calcinations between 550° and 900°, nearly all the calcium oxide is produced within the first few minutes, yet decomposition is not quite complete even after 5 hr., the volatile-matter contents of the samples generally showing temperature variations

FIG. 3. *Samples heated* in vacuo *at* 350° *and* 450°.



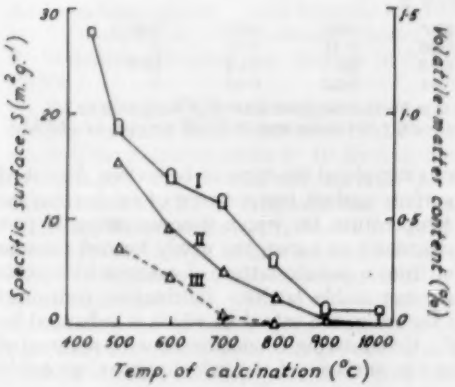


FIG. 4. *Calcination of calcium hydroxide heated for 5 hr. in air.*

I, Specific surface calc. from :
□ N_2 isotherms, ○ O_2 isotherms.
II, Total volatile-matter content.
III, Water content.

similar to those of S in Fig. 4. This suggests that, as for magnesium oxide, the rate of sintering is controlled by the removal of traces of water and carbon dioxide chemisorbed on the surface of the micro-regions; indications of a break in the specific surface curve at 700° are probably caused by the rate of sintering being mainly dependent on removal of water below this temperature and of carbon dioxide above (cf. Fig. 4), a larger energy of activation for the latter process causing greater proportionate decreases in S between 700° and 900°. The higher volatile-matter contents (w) of the samples calcined at 450° and 500° (Table 1) partly arise from carbonation of small amounts of the calcium oxide during calcination (since the dissociation pressure of calcium carbonate is less than the partial pressure of atmospheric carbon dioxide); these samples have remarkably *lower* specific surface areas than those calcined *in vacuo* for 5 hr., although over 97% of the calcium hydroxide is decomposed in all cases (Table 1). Similar differences in S are also shown

when the decomposition is far from complete, *e.g.*, at 40% decomposition in air and *in vacuo* at 450°, S = 14·1 and 35·5 $m.^2 g.^{-1}$, respectively.

The last results appear contrary to expectation in that the calcium oxide is produced more slowly in air than *in vacuo* at the same temperature and subsequently has shorter time in which to sinter. During the decomposition in air, however, the water-vapour

TABLE 1.

Temp. of calcination	S ($m.^2 g.^{-1}$) for samples calcined in: air	S ($m.^2 g.^{-1}$) for samples calcined in: vacuum	w (%) for samples calcined in: air, H_2O (%)	w (%) for samples calcined in: air, CO_2 (%)	w (%) for samples calcined in: vacuum, H_2O (%)	w (%) for samples calcined in: vacuum, CO_2 (%)
450°	28·0	72·2	0·92	3·35	0·05	0·29
500	18·6	65·0	0·36	0·41	0	0·29

concentration gradients along the capillary passages in the product will probably be smaller, giving lower rates of nucleation in the recrystallisation of the calcium oxide pseudo-lattice, and thus smaller increases in the number of calcium oxide micro-regions and in S than in the " vacuum " experiments; the greater average micro-region size of the calcium oxide is indicated by the absence of line-broadening in the X-radiograms of the sample decomposed in air at 450°. Nucleation may also be inhibited in air by the surface layer of chemisorbed carbonate and of water (probably present as hydroxyl groups on the surface rather than as bulk calcium hydroxide). *In vacuo*, atmospheric carbon dioxide is excluded and the water vapour evolved is rapidly removed so that recombination with the newly formed calcium oxide is minimised. The last traces of water are, however, still held with considerable tenacity (Table 2). But the proportion of solid surfaces covered by this residual water, θ, is small and can have little effect on the rate of nucleation.

TABLE 2.

Temp. of calcination	350°	400°	450°	500°
Water content (%)	0·66	0·24	0·05	0
S * ($m.^2 g.^{-1}$)	96·8	90·9	93·3	82·7
θ †	0·34	0·13	0·03	0

* Measured when the rate of decomposition first became inappreciable (<0·01% in 5 hr.).
† One molecule of residual water assumed to occupy the same area as 2 OH groups, *i.e.*, 15 Å².

Conclusion.—The calcination of lime is an example of the type of behaviour described in Part I,[1] in which the curves of specific surface against temperature of calcination for fixed times show maxima at or near the temperature for which decomposition is just complete. At temperatures below 500°, particularly *in vacuo*, the newly formed calcium oxide becomes activated by recrystallisation from a pseudo-lattice of calcium hydroxide to very small individual crystals having a more stable lattice. Calcination continued after complete decomposition always causes sintering, the extent of which is enhanced by increase in temperature at least up to 1000°; the sintering is concurrent with removal of chemisorbed water and carbon dioxide from the surfaces of the micro-regions, probably as they adhere.

The author thanks Dr. S. J. Gregg for bringing this problem to his notice and for several discussions; Dr. G. H. Manning, of Imperial Chemical Industries Limited, for taking the X-ray photographs; the University of London Research Fund for the loan of apparatus; and the Imperial Chemical Industries Research Fund for a grant for apparatus.

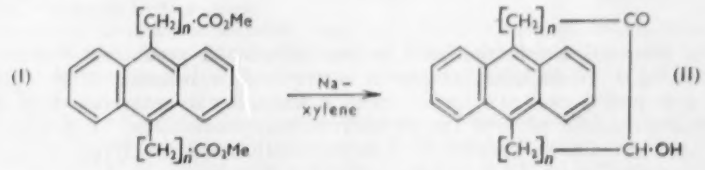
TECHNICAL COLLEGE, PLYMOUTH. [*Received, October 5th*, 1955.]

301. *A New Method for the Preparation of* 9 : 10-*Disubstituted Anthracenes.*

By K. Jasper Clark.

9 : 10-Disubstituted 9 : 10-dihydro-9 : 10-dihydroxyanthracenes, obtained by the action of Grignard reagents upon anthraquinone, can be conveniently reduced by phenylhydrazine in acetic acid to 9 : 10-disubstituted anthracenes in good yield.

9 : 10-Di-(ω-carboxyalkyl)anthracenes were required for attempted acyloin ring-closures of their dimethyl esters (I; $n > 3$), and the consequent production of bridges across the 9 : 10-positions of anthracene (II), but no general method for the synthesis of such acids has been published.



The reaction of 9 : 10-dihydro-9 : 10-disodioanthracene with ω-halogeno-esters failed to produce any hydrolysable material, possibly because of acylation of the disodio-compound analogous to that reported for ethyl benzoate.[1] Clearly, a halide is required which bears on the ω-position a relatively inert system which is capable of being converted into a carboxy-group. Allyl bromide has been employed successfully to give a 35% yield of 9 : 10-diallyl-9 : 10-dihydroanthracene. However, oxidation of this compound to 9 : 10-diallylanthracene, by the use of benzoquinone or chloranil, gave only very poor yields.

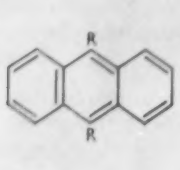
Accordingly, Grignard reagents bearing ω-olefinic and ω-ethereal groups, capable of further reaction, have been examined for activity towards anthraquinone, and a study made of the reduction of the 9 : 10-disubstituted 9 : 10-dihydro-9 : 10-dihydroxyanthracenes so obtained. The method of Cook *et al.*[2] for the reaction of anthraquinone with twice the calculated quantity of Grignard reagents gave reproducible yields of the desired diols. Hitherto, the most generally successful reduction of such diols has been to shake their dimethyl ethers with an alkali metal for several days.[3] This method failed with 9 : 10-diallyl-9 : 10-diethoxy-9 : 10-dihydroanthracene, potassium or sodium being used, but it was found that such diols, or their ethereal derivatives, could be reduced smoothly by phenylhydrazine in acetic acid in ½ hr. The yields of 9 : 10-disubstituted anthracenes (III) from diprimary alkylanthracenediols are of the order of 60%.

9 : 10-Diallyl-9 : 10-dihydro-9 : 10-dihydroxyanthracene, prepared by Cook *et al.*[2] in unquoted yield, was obtained in 73% yield from allylmagnesium bromide, and found to exist in two isomeric forms, which were easily separated after methylation or ethylation. Both diethyl derivatives absorb at 10·09 μ and 10·95 μ (allyl), and at 9·4 μ (ethoxy). The mixture of diallylanthracenediols, and both dimethyl and diethyl ethers, reacted with phenylhydrazine in acetic acid to give a 65% yield of 9 : 10-diallylanthracene, absorbing at 10·09 μ and 10·95 μ (allyl), and identical with the product obtained from 9 : 10-dihydro-9 : 10-disodioanthracene. The best results were obtained by mixing the reactants in the cold, warming the solution rapidly until nitrogen was evolved, and finally refluxing for ¼ hr. Addition of the diol to a boiling solution of phenylhydrazine in acetic acid lowered the yield to 31%, and the major product was a yellow powder, m. p. 195°; the spectral and

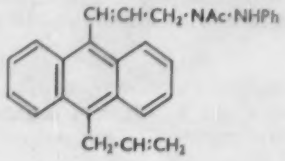
[1] Lerer, *Ann. Combustibles liquides*, 1933, **8**, 681.
[2] Cook, Dodds, and Lawson, *Proc. Roy. Soc.*, 1936—1937, *B*, **121**, 133.
[3] Bachmann and Chemerda, *J. Org. Chem.*, 1939, **4**, 583.

analytical evidence suggested that this material was 9-(3-*N*-acetyl-*N'*-phenylhydrazinopropenyl)-10-allylanthracene (IV), resulting from a 1 : 7-anionotropic rearrangement, during the reduction of the diallylanthracenediol.

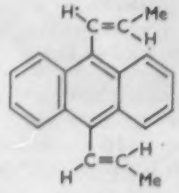
9 : 10-Diallylanthracene was isomerised smoothly to the 9 : 10-dipropenyl compound, which absorbs at 10·33 μ and must therefore contain the most sterically probable *trans*-H configuration of the two double bonds (V). Bromination of both anthracenes, by either



(III)



(IV)



(V)

bromine or *N*-bromosuccinimide, failed to yield identifiable products. However, hydrobromination of 9 : 10-diallylanthracene in acetic acid or benzene, in the presence of peroxide, gave a 90% yield of a dihydrobromide, which has an anthracene-type ultraviolet absorption and must therefore be a 9 : 10-bisbromopropylanthracene. It is hoped that this product is, in fact, the ωω'-dibrominated dipropylanthracene, which can be converted by standard reactions into 9 : 10-di-(4-carboxylbutyl)anthracene.

3-Ethoxypropylmagnesium bromide gave a 60% yield of 9 : 10-di-(3-ethoxypropyl)-9 : 10-dihydro-9 : 10-dihydroxyanthracene.

9 : 10-Dihydro-9 : 10-dihydroxy-9 : 10-diundecenylanthracene was prepared in 10% yield from undecenylmagnesium chloride, and gave a 67% yield of 9 : 10-diundecenylanthracene by the phenylhydrazine method. The three allyl absorption peaks of 5·42 μ, 10·09 μ, and 10·95 μ are all clearly shown in this anthracene.

3-Phenoxypropyl bromide and 4-phenoxybutyl bromide failed to yield recognisable addition products with anthraquinone in the Grignard reaction. The former reacted with magnesium in ether to give some gas, presumably *cyclo*propane,[4] and phenoxymagnesium bromide. In addition, 1 : 6-diphenoxyhexane was isolated in small yield, after attempted reaction with anthraquinone. The liberation of phenoxymagnesium bromide did not take place in the preparation of 4-phenoxybutylmagnesium bromide, and a clear Grignard solution was obtained. This reagent has been reported to give a 30% yield of alcohol with benzophenone,[5] but only 1 : 8-diphenoxyoctane was isolated after attempted reaction with anthraquinone.

Secondary alkylmagnesium halides gave poor or no yields of 9 : 10-dialkyl-9 : 10-dihydro-9 : 10-dihydroxyanthracenes. *iso*Propylmagnesium chloride gave only a 5% yield of the expected diol, and the bromide no yield. Reduction by phenylhydrazine gave a 29% yield of 9 : 10-di*iso*propylanthracene, absorbing at 7·35 μ. *cyclo*Hexylmagnesium bromide reacted with anthraquinone to give an unidentified oil, which would not distil, form solid ethers, or undergo reduction by phenylhydrazine. Steric effects, and the well-known reducing power of *cyclo*hexylmagnesium halides,[6] undoubtedly complicate this reaction. Cook *et al.*,[2] however, report the isolation of 9 : 10-dihydro-9 : 10-dihydroxy-9 : 10-di*cyclo*pentylanthracene by the Grignard method.

As a model preparation, 9 : 10-dimethylanthracene was prepared in 57% yield (overall) from anthraquinone by combination of the Grignard and the phenylhydrazine reduction method.

Experimental

9 : 10-*Diallyl*-9 : 10-*dihydroanthracene*.—A mixture of anthracene (50 g.), broken glass (20 g.), dry ether (600 ml.), and sodium powder (34·5 g.) was shaken under nitrogen for 3 days, and

[4] Gragson, Greenlee, Derfer, and Boord, *ibid.*, 1955, **20**, 275.
[5] Benoit, Delavigne, and Eliopoulo, *Ann. Pharm. franç.*, 1952, **10**, 181.
[6] Sabatier and Mailhe, *Compt. rend.*, 1905, **141**, 298.

allyl bromide (72 g.) then added dropwise, with vigorous stirring and external cooling. Finally, the mixture was refluxed for 2 hr., cooled, and filtered, the residue being washed with dry ether (2 × 100 ml.). The combined ethereal solutions were washed with dilute hydrochloric acid, sodium carbonate solution, and water, dried (Na_2SO_4), and evaporated. The residual viscous oil was dissolved in light petroleum (b. p. 60—80°), and kept for 3 days. After filtration, the solution was distilled, and the pale yellow fraction, b. p. 160—170°/2—3 mm., collected (25·7 g., 35%). For analysis, this *compound* was redistilled at 110—112°/0·04 mm., and a small portion again distilled from a bulb (Found : C, 91·9; H, 7·6. $C_{20}H_{20}$ requires C, 92·3; H, 7·7%).

Oxidation of 9 : 10-*Diallyl*-9 : 10-*dihydroanthracene.*—This product (10·6 g.) and *p*-benzoquinone (8·8 g.) were refluxed for 3 hr. in dry xylene (100 ml.). After cooling overnight, the solution was filtered and evaporated to a tarry residue, which deposited a little solid during several days. This was crystallised repeatedly from alcohol (charcoal), to give light yellow needles of the *diallylanthracene*, m. p. 135·5°, strongly fluorescent in alcohol and benzene (Found : C, 92·8; H, 7·1. $C_{20}H_{18}$ requires C, 93·0; H, 7·0%). Light absorption : $\lambda_{max.}$ 2600, 3400, 3580, 3750, and 4000 Å (ε 25,500, 2240, 4960, 7290, and 7480 respectively). Absorption also occurred at 10·09 μ and 10·95 μ (allyl).

No improvement in yield was found on lengthening the reaction time, or substituting chloranil for benzoquinone. A maleic anhydride *adduct* was prepared in xylene, and crystallised thereform as white needles, m. p. 240° (decomp.) (Found : C, 81·1; H, 5·5. $C_{24}H_{20}O_3$ requires C, 80·9; H, 5·6%).

9 : 10-*Diallyl*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene.*—This compound was prepared, with certain modifications, according to the procedure of Cook *et al.*[8] A solution of allylmagnesium bromide was prepared [7] by adding allyl bromide (121 g.), in dry ether (500 ml.), dropwise to magnesium turnings (72 g.) and ether (300 ml.), with vigorous stirring. The rate of addition was adjusted to give a steady reflux (2—3 hr.). Stirring was continued for 2 hr., ether (500 ml.) added, and the ethereal solution decanted from excess of magnesium into a second flask. At 0°, and under vigorous stirring, anthraquinone (52 g.) was added in small portions (½ hr.). The stirring was continued for 3 hr., and the mixture stored overnight, a dark oil separating from the green ethereal solution. Decomposition was effected with concentrated ammonium chloride solution, with cooling, and the ethereal solution of the product was washed with water, and separated from any precipitated anthraquinone. On distillation, an oil remained, which crystallised on cooling. This was dissolved in hot benzene and shaken with boiling sodium hydrosulphite (dithionite) solution until the lower, aqueous layer was colourless. The benzene solution was dried (Na_2SO_4) and distilled, yielding a light yellow oil which crystallised on trituration with light petroleum (b. p. 60—80°). Recrystallisation from this solvent gave a mixture of the *cis*- and the *trans*-diol, m. p. 100—110° (53·3 g., 73%).

α- *and* β-9 : 10-*Diallyl*-9 : 10-*dihydro*-9 : 10-*dimethoxyanthracene.*—9 : 10-Diallyl-9 : 10-dihydro-9 : 10-dihydroxyanthracene (5·4 g.) in dry methanol (20 ml.) was shaken with methanol (5 ml.) containing sulphuric acid (5 drops). A fine white solid was precipitated at once, and was filtered off and washed with aqueous ammonia and methanol. The α-*dimethoxy-compound* was insoluble in methanol, and was crystallised several times from benzene, forming fine white crystals (1·5 g.), m. p. 184° (Found : C, 82·7; H, 7·5. $C_{22}H_{24}O_2$ requires C, 82·5; H, 7·5%).

¼ Hr. after deposition of the α-compound, macro-crystals began to be deposited, and this was allowed to proceed for ¼ hr. The β-*compound* was filtered off and washed as before; it crystallised from methanol as long white needles (2·3 g.), m. p. 92·5° (Found : C, 82·4; H, 7·6%).

α- *and* β-9 : 10-*Diallyl*-9 : 10-*diethoxy*-9 : 10-*dihydroanthracene.*—These two isomers were prepared, in the same manner as the methyl analogues, from ethanol, but reaction was slower. Deposition of the α-*isomer* occurred only after ¼ hr., and the fine white deposit was washed and crystallised from ethanol, small white crystals, m. p. 126°, being obtained (Found : C, 82·7; H, 8·1. $C_{24}H_{28}O_2$ requires C, 82·7; H, 8·0%). The β-*form* was deposited only after 2 hr., and crystallised from ethanol as long white needles, m. p. 76° (Found : C, 82·5; H, 8·0%). Light absorption : both isomers absorbed at 9·4 μ (ethoxy), and at 10·09 and 10·95 μ (allyl).

9 : 10-*Diallylanthracene.*—All four of the above dimethyl and diethyl ethers reacted, as the diol mixture below, to yield 9 : 10-diallylanthracene. The alkali-metal dealkoxylation [9] failed in the one instance in which it was tried, *viz.*, on the α-diallyldiethoxy-compound. A mixture of 9 : 10-diallyl-9 : 10-dihydro-9 : 10-dihydroxyanthracene (32·2 g.), phenylhydrazine (60 ml.), and glacial acetic acid (260 ml.) was heated on the water-bath until the evolution of nitrogen

[7] Gilman and McGlumphy, *Bull. Soc. chim. France*, 1928, **43**, 1322.
[8] Gensler, Behrmann, and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 1071.
[9] Anderson, Crawford, and Sherrill, *ibid.*, 1946, **68**, 1294.

ceased (½ hr.), and then refluxed for ½ hr. Long yellow needles of 9 : 10-*diallylanthracene* crystallised from the mixture, and were washed with a little acetic acid and ethanol (18·7 g., 65·7%). For analysis, the compound was recrystallised from alcohol (charcoal) several times to give light yellow needles, m. p. 135·5° (Found : C, 92·9; H, 7·1. $C_{20}H_{18}$ requires C, 93·0; H, 7·0%).

Yields of 9 : 10-diallylanthracene were halved when the diallyl-diol was added, in small portions, to a boiling solution of phenylhydrazine in acetic acid. The main product was an amorphous yellow powder, which was recrystallised repeatedly from alcohol for analysis, m. p. 195°. Spectroscopic and analytical data indicated that it was 9-(3-N-*acetyl*-N′-*phenylhydrazinopropenyl*)-10-*allylanthracene* (Found : C, 83·0; H, 6·5; N, 6·75. $C_{25}H_{26}ON_2$ requires C, 82·75; H, 6·4; N, 6·8%). Light absorption : $\lambda_{max.}$ 2600, 3250, 3625, 3770, and 4000 Å (ε 30,000, 1290, 4400, 6600, and 6200, respectively). Absorption also occurred at 3·1 (NH), 6·01 (amide), 10·33 (*trans*-H), and 10·1 and 11·0 μ (allyl).

9 : 10-*Dipropenylanthracene.*—9 : 10-Diallylanthracene (3·35 g.) was heated at reflux temperature with ethanol (120 ml.) and potassium hydroxide (10 g.) for 12 hr. Green needles of the isomeric *propenyl compound* crystallised and were filtered off and washed with hot water (yield >90%). Recrystallisation from alcohol (charcoal) gave pale green needles, m. p. 166° (Found : C, 92·7; H, 6·9. $C_{20}H_{18}$ requires C, 93·0; H, 7·0%). Light absorption : $\lambda_{max.}$ 2550, 3850, and 4000 Å (ε 24,000, 10,200, and 9300, respectively). Absorption also occurred at 10·33 μ (*trans*-H).

9 : 10-*Di*-(x-*bromopropyl*)*anthracene.*—Glacial acetic acid (100 ml.) was saturated at below 10° with hydrobromic acid, from a tetralin generator, and perphthalic acid (0·1 g.) added. 9 : 10-Diallylanthracene (5 g.) was added, and the mixture warmed. As the unsaturated compound dissolved, reaction took place, and finally the evolution of hydrobromic acid ceased as the solution refluxed. Dark green crystals were deposited when the mixture cooled, and these were separated and crystallised from alcohol (1 l.) (yield, 7·3 g., 90%). The *di*(*bromopropyl*)-*anthracene* was recrystallised several times for analysis, forming light green needles, m. p. 181·5° (Found : C, 57·0; H, 4·9; Br, 38·2. $C_{20}H_{20}Br_2$ requires C, 57·1; H, 4·8; Br, 38·1%). Light absorption : $\lambda_{max.}$ 2600, 3425, 3600, 3800, and 4000 Å (ε 34,300, 4480, 9330, 14,000, and 14,360, respectively).

9 : 10-*Dihydro*-9 : 10-*dihydroxy*-9 : 10-*diundecenylanthracene.* Undecenyl chloride [8] (27 g.) in dry ether (70 ml.) was added dropwise to magnesium (3·4 g.) in ether (15 ml.). A small amount of allyl bromide was needed to initiate the reaction. The Grignard solution was then cooled to 0°, ether (150 ml.) added, and anthraquinone (7·42 g.) dropped in to the well-stirred solution at once. Stirring was continued at room temperature for 1 hr., and then under reflux for 3 hr. After the usual decomposition and extraction, an oil remained which crystallised from light petroleum (b. p. 60—80°) as white plates, m. p. 88° (1·85 g., 10%). A good analysis could not be obtained.

9 : 10-*Dihydro*-9 : 10-*dimethoxy*-9 : 10-*diundecenylanthracene.*—This *ether*, prepared as for the diallyl compound, crystallised from methanol; it had m. p. 77° (Found : C, 83·7; H, 10·3. $C_{38}H_{56}O_2$ requires C, 83·8; H, 10·3%).

9 : 10-*Diundecenylanthracene.*—The foregoing ether (0·8 g.) was treated with phenylhydrazine (1·5 ml.) and glacial acetic acid (6 ml.) in the manner described above. An oil separated during the refluxing period, but, on cooling, this solidified, and was separated and crystallised from ethanol, to give fine yellow-green needles (0·5 g., 67%), m. p. 70° (Found : C, 89·6; H, 10·5. $C_{34}H_{50}$ requires C, 89·6; H, 10·4%). Light absorption : $\lambda_{max.}$ 2600, 3425, 3600, 3800, and 4025 Å (ε 61,000, 3300, 7000, 11,900, and 11,200, respectively). Absorption also occurred at 5·42, 10·0, and 11·0 μ (allyl).

9 : 10-*Di*-(3-*ethoxypropyl*)-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene.*—3-Ethoxypropyl bromide [9] (54·5 g.) in dry ether (160 ml.) was added dropwise to magnesium (7·8 g.) in ether (50 ml.), at such a rate that moderate refluxing was maintained. A crystal of iodine and warming were both necessary to initiate the reaction. After the dissolution of the metal, the solution was kept for ½ hr., and then, with vigorous stirring at 0°, anthraquinone (16·9 g.) was added in small portions. A solid Grignard complex settled out. The solution was stirred for 3 hr., and finally refluxed for 2 hr. The usual procedure was followed for the isolation of the product, and, on treatment of the residual oil with light petroleum (b. p. 60—80°), the diol (17 g., 61%), m. p. 111—112° was precipitated, but could not be obtained analytically pure.

9 : 10-*Di*-(3-*ethoxypropyl*)-9 : 10-*dihydro*-9 : 10-*dimethoxyanthracene.*—This *ether* was obtained from the acid-catalysed reaction of methanol with the diol, in the usual manner; crystallised from methanol it had m. p. 153·5° (Found : C, 75·9; H, 8·6. $C_{26}H_{34}O_4$ requires C, 75·7; H, 8·7%).

9 : 10-*Diethoxy*-9 : 10-*di*-(3-*ethoxypropyl*)-9 : 10-*dihydroanthracene*.—The use of ethanol in the previous preparation gave the *diethoxy-ether*, m. p. 93·5° (Found : C, 76·1; H, 9·1. $C_{32}H_{46}O_4$ requires C, 76·4; H, 9·1%).

9 : 10-*Diisopropylanthracene*.—*iso*Propyl chloride (39·25 g.) was treated with magnesium (12 g.) in ether (300 ml.). Anthraquinone (26 g.) was added in the usual manner, and the product isolated as before. Only 1·9 g. of 9 : 10-dihydro-9 : 10-dihydroxy-9 : 10-di*iso*propylanthracene were obtained (5%). This was treated with phenylhydrazine (4 ml.) and acetic acid (12 ml.), to yield green-yellow crystals (0·5 g., 29%) of the *anthracene*. Recrystallisation from alcohol gave light green crystals, m. p. 172° (Found : C, 91·5; H, 8·2. $C_{20}H_{22}$ requires C, 91·6; H, 8·2%). Light absorption : $\lambda_{max.}$ 2600, 3420, 3600, 3800, and 4000 Å (ε 25,600, 2500, 5370, 8300, and 9560, respectively). Absorption also occurred at 7·35 μ (*iso*propyl).

9 : 10-*Dimethylanthracene*.—Methyl iodide (17·7 g.) was treated with magnesium (3 g.) in ether (75 ml.), and anthraquinone (5·2 g.) added. After isolation, the dimethylanthracenediol was caused to react with phenylhydrazine (8 ml.) and acetic acid (35 ml.). From this reaction yellow crystals (2·9 g., 57% overall), m. p. 180°, were obtained.

Some analyses were performed by Mr. F. Hall. The author thanks Sir Robert Robinson for his interest and advice.

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302. *Carcinogenic Nitrogen Compounds. Part XVIII.* The Synthesis of Some Polycyclic Carbazoles.*

By NG. PH. BUU-HOÏ and PIERRE JACQUIGNON.

New syntheses are reported for some known polycyclic carbazoles, and several new highly condensed carbazoles and their thiophen analogues have been prepared for biological evaluation of potential carcinogenic or carcinostatic activity.

WHEREAS among aromatic hydrocarbons and in the acridine group significant carcinogenic activity is already encountered in tetracyclic derivatives (*e.g.*, 1 : 2-benzanthracenes and 1 : 2-benzacridines), in the carbazole series pronounced activity is reached only with pentacyclic molecules (*e.g.*, 3 : 4-5 : 6-dibenzocarbazole).[1] This suggested the preparation of further carbazoles having five or more rings, and their testing for carcinogenic, and the related tumour-growth inhibiting, activity.

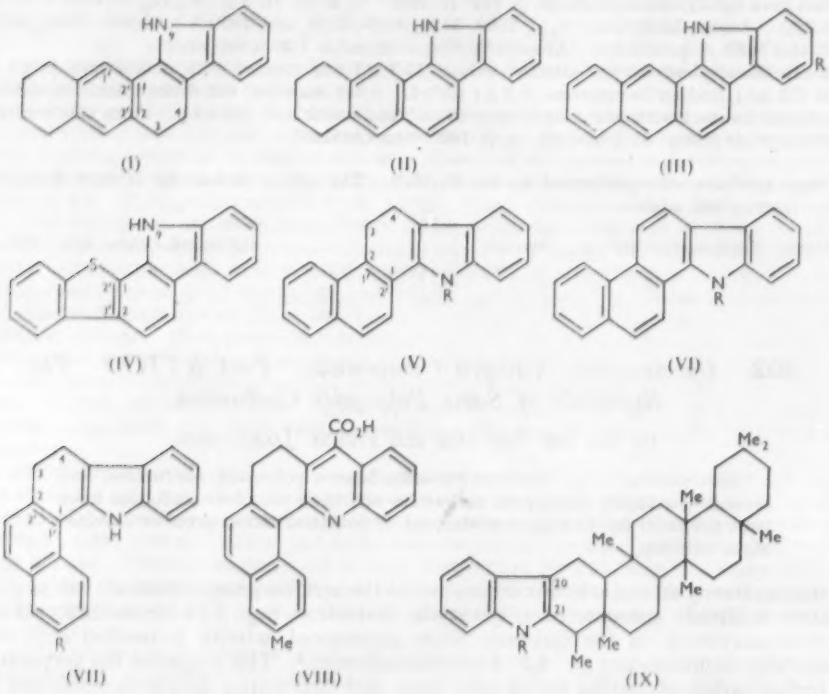
Naphtho(2′ : 3′-1 : 2)carbazole (III; R = H), first synthesised by von Braun and Bayer,[2] was now prepared by Fischer cyclisation of the phenylhydrazone of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene, and dehydrogenation of the resulting 3 : 4 : 5′ : 6′ : 7′ : 8′-hexahydronaphtho(2′ : 3′-1 : 2)carbazole (I) with chloranil in excess; when only 1 mol. of chloranil was used, partial dehydrogenation occurred, and the 5′ : 6′ : 7′ : 8′-tetrahydro-derivative (II) was obtained. 6-Methylnaphtho(2′ : 3′-1 : 2)-carbazole (III; R = Me) was prepared in the same way. Thionaphtheno(2′ : 3′-1 : 2)-carbazole (IV; R = H) and its 6-methyl derivative (IV; R = Me), thiophen isologues of (III) with very similar properties, were obtained from 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen. Another group of pentacyclic derivatives of carbazole was prepared from 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene; the phenylhydrazone of this ketone underwent cyclisation to 3 : 4-dihydronaphtho(2′ : 1′-1 : 2)carbazole (V; R = H), which was

* Part XVII, Buu-Hoï, Royer, and Hubert-Habart, *J.*, 1955, 1082.

[1] Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Badger, Cook, Kennaway, Kennaway, Martin, and Robinson, *ibid.*, 1942, **131**, 170; Kirby and Peacock, *Brit. J. Exp. Path.*, 1946, **27**, 179; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.

[2] Von Braun and Bayer, *Annalen*, 1929, **472**, 101.

dehydrogenated by chloranil to the naphthocarbazole (VI; R = H). The phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene was indolised to 3 : 4-dihydronaphtho(1′ : 2′-1 : 2)carbazole (VII; R = H), whose low melting point contrasted with the high melting point of its isomer (V; R = H); the methyl compound (VII; R = Me), similarly prepared, likewise had a very low melting point. It is interesting that, in the acridine series of analogous structure, the cinchoninic acid (VIII), obtained from the same ketone by a Pfitzinger reaction, has a normal melting point.



(I) (II) (III) (IV) (V) (VI) (VII) (VIII) (IX)

N-Alkylphenylhydrazines proved convenient for the synthesis of polycyclic 9-alkylcarbazoles; thus, 9-methylnaphtho(2′ : 1′-1 : 2)carbazole (VI; R = Me) was readily prepared *via* the 3 : 4-dihydro-compound (V; R = Me). This method, applied to the preparation of the carcinogenic 9-methyl-1 : 2-benzocarbazole, was an improvement on the previous *N*-methylation procedure.[3]

Two heptacyclic compounds of the same series, indolo(3′ : 2′-20 : 21)friedelene (IX; R = H) and its 1′-methyl derivative (IX; R = Me), were prepared by indolisation of the phenylhydrazone and *N*-methylphenylhydrazone of friedelin, a saturated ketone extracted from cork.[4]

During this work, it was observed that compounds of the carbazole series form well-crystallised, deeply coloured addition complexes with one mol. of tetrachlorophthalic anhydride,[5] and these complexes are often more suitable for characterisation than the picrates.

The new carbazoles reported here are under biological examination in this Institute (Dr. Zajdela) for carcinogenic activity.

[3] Buu-Hoï, *J.*, **1946**, 795.
[4] Drake and Jacobsen, *J. Amer. Chem. Soc.*, 1935, **57**, 1570; Ruzicka, Jeger, and Ringnes, *Helv. Chim. Acta*, 1944, **27**, 972; Dutler, Jeger, and Ruzicka, *ibid.*, 1955, **38**, 1268.
[5] Cf. Pfeiffer, *Ber.*, 1922, **55**, 413; Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056.

Experimental

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydronaphtho*(3′ : 2′-1 : 2)*carbazole* (I).—A mixture of phenylhydrazine (2 g.) and **1 : 2 : 3 : 4 : 5 : 6 : 7 : 8**-octahydro-1-oxoanthracene (2 g.; prepared from tetralin and succinic anhydride [6]) was heated at 120—130° until water ceased to be evolved, and the crude hydrazone was heated with an acetic acid solution of hydrogen chloride (20 c.c.) for a few seconds. After cooling, water was added, and the cyclisation *product* taken up in benzene; recrystallisation from *cyclo*hexane afforded leaflets (2 g.), m. p. 215°, giving a yellow halochromy in sulphuric acid and a dark violet picrate (Found: C, 87·6; H, 6·9. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0%).

5′ : 6′ : 7′ : 8′-*Tetrahydronaphtho*(2′ : 3′-1 : 2)*carbazole* (II).—A solution of the foregoing hexahydro-compound (5 g.) in dry xylene (100 c.c.) was refluxed with chloranil (5 g.) for 12 hr. After cooling, the precipitated tetrachloroquinol was filtered off, and the xylene layer washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The residue left on evaporation of the solvent crystallised as grey-tinged needles (3 g.), m. p. 273°, from *cyclo*hexane (Found: C, 88·3; H, 6·2. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3%). This *carbazole* gave a violet picrate and a deep yellow halochromy in sulphuric acid.

Naphtho(2′ : 3′-1 : 2)*carbazole* (III).—The foregoing tetrahydro-compound (5 g.) was dehydrogenated with chloranil (15 g.) in xylene (100 c.c.) as above. The dehydrogenation product formed pale yellow leaflets (3·5 g.), m. p. 327°, from *cyclo*hexane and gave an orange-yellow halochromy in sulphuric acid; von Braun and Bayer [3] gave m. p. 325°.

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydro*-6-*methylnaphtho*(2′ : 3′-1 : 2)*carbazole*.—A solution of **1 : 2 : 3 : 4 : 5 : 6 : 7 : 8**-octahydro-1-oxoanthracene (4 g.), *p*-tolylhydrazine hydrochloride (3·6 g.), and sodium acetate (2·6 g.) in ethanol was refluxed for 1 hr., and the crude *p*-tolylhydrazone which was precipitated on dilution with water was collected and indolised in the usual way. The resulting ***hexahydrocarbazole*** formed prisms (3·5 g.), m. p. 242°, from *cyclo*hexane and gave a lemon-yellow halochromy in sulphuric acid and a violet picrate (Found: C, 87·6; H, 7·4. $C_{21}H_{21}N$ requires C, 87·8; H, 7·3%).

6-*Methylnaphtho*(2′ : 3′-1 : 2)*carbazole* (III; R = Me).—Dehydrogenation of the foregoing compound (1·5 g.) with chloranil (4·4 g.) afforded a *carbazole*, crystallising from *cyclo*hexane as pale yellow needles (1 g.), m. p. >340° (Found: C, 89·5; H, 5·3. $C_{21}H_{15}N$ requires C, 89·7; H, 5·3%).

Thionaphtheno(2′ : 3′-1 : 2)*carbazole* (IV; R = H).—The crude hydrazone from **1 : 2 : 3 : 4**-tetrahydro-1-oxodibenzothiophen [7] (1·5 g.) and phenylhydrazine (2·4 g.) underwent partial decomposition on indolisation; the crude product yielded, on dehydrogenation with chloranil (1 g.), a *carbazole*, crystallising as colourless, sublimable leaflets (from benzene), m. p. >340°, giving an orange-yellow halochromy with sulphuric acid (Found: C, 78·8; H, 4·5. $C_{18}H_{13}NS$ requires C, 78·5; H, 4·7%).

6-*Methylthionaphtheno*(2′ : 3′-1 : 2)*carbazole* (IV; R = Me).—Similarly prepared from *p*-tolylhydrazine hydrochloride (2·5 g.), and dehydrogenation of the intermediary dihydrocarbazole (1·2 g.) with chloranil (1·2 g.), this *compound* formed colourless, sublimable leaflets (from benzene), m. p. and halochromy as for its analogue (Found: C, 79·1; H, 5·0. $C_{19}H_{15}NS$ requires C, 78·9; H, 5·2%).

3 : 4-*Dihydronaphtho*(2′ : 1′-1 : 2)*carbazole* (V; R = H).—A mixture of **1 : 2 : 3 : 4**-tetrahydro-1-oxophenanthrene [8] (5 g.) and phenylhydrazine (5 g.) was heated at 120—130° for a few minutes, and the crude hydrazone indolised in the usual way. The *dihydro-compound* (5 g.) formed colourless needles, m. p. 281°, from ethanol–benzene (Found: C, 88·9; H, 5·7. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%). *Naphtho*(2′ : 1′-1 : 2)*carbazole* (VI; R = H), obtained on dehydrogenation with chloranil, formed yellowish, sublimable prisms, m. p. >340°, from ethanol (Found: C, 89·7; H, 5·0. $C_{20}H_{13}N$ requires C, 89·9; H, 4·9%); its picrate formed dark violet needles, m. p. 193—194°, from ethanol.

3 : 4-*Dihydro*-9-*methylnaphtho*(2′ : 1′-1 : 2)*carbazole* (V; R = Me).—A mixture of the oxophenanthrene (2 g.) and *N*-methylphenylhydrazine (2 g.) was heated at 120°; the crude hydrazone yielded on indolisation a *dihydro-compound* (1·4 g.), crystallising as yellowish needles, m. p. 198°, from light petroleum (Found: C, 89·2; H, 6·1. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%). This gave a picrate which crystallised as dark violet needles, m. p. 192—193° (darkening

[6] Cf. Buu-Hoï and Jacquignon, *J.*, 1954, 513.
[7] Buu-Hoï and Cagniant, *Ber.*, 1943, **76**, 1269.
[8] Haworth, *J.*, 1932, 1125.

above 180°), from ethanol, and a stable *addition complex* with tetrachlorophthalic anhydride which crystallised as red needles, m. p. 183—184°, from acetic acid (Found: C, 60·9; H, 3·3. $C_{29}H_{17}O_3NCl_4$ requires C, 61·2; H, 3·0%).

9-*Methylnaphtho*(2′ : 1′-1 : 2)*carbazole* (VI; R = Me).—A solution of the foregoing dihydro-compound (1 g.) and chloranil (1 g.) in xylene was refluxed for 3 hr. The dehydrogenation *product* formed yellowish leaflets, m. p. 268° (from *cyclo*hexane) (Found: C, 89·5; H, 5·2. $C_{21}H_{15}N$ requires C, 89·7; H, 5·3%), giving a violet picrate.

3 : 4-*Dihydro*-9-*methyl*-1 : 2-*benzocarbazole*.—Obtained from α-tetralone (2 g.) and *N*-methylphenylhydrazine (2 g.), this compound crystallised as colourless leaflets, m. p. 134°, from ethanol (Found: C, 87·8; H, 6·5. Calc. for $C_{17}H_{15}N$: C, 87·6; H, 6·4%); the picrate decomposed on recrystallisation, but the addition product with one mol. of tetrachlorophthalic anhydride formed stable red needles, m. p. 121—122°, from acetic acid. Dehydrogenation of this dihydro-compound with chloranil (12 hours' heating) afforded a 78% yield of 9-methyl-1 : 2-benzocarbazole, m. p. 169°, from *cyclo*hexane (lit.,[8] m. p. 168°).

3 : 4-*Dihydronaphtho*(1′ : 2′-1 : 2)*carbazole* (VII; R = H).—1 : 2 : 3 : 4-Tetrahydro-4-oxophenanthrene[8] (2 g.) was condensed with phenylhydrazine (2 g.); the crude hydrazone gave on indolisation a resin which was purified *via* its picrate (brown-violet needles, m. p. 176°, from methanol). Decomposition of this picrate (1·5 g.) with aqueous ammonia, and repeated crystallisation of the free *dihydrocarbazole* from light petroleum, afforded colourless needles, m. p. 118° (Found: C, 89·5; H, 5·5. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%).

3 : 4-*Dihydro*-6′-*methylnaphtho*(1′ : 2′-1 : 2)*carbazole* (VII; R = Me), prepared from 1 : 2 : 3 : 4-tetrahydro-7-methyl-4-oxophenanthrene (2 g.) and phenylhydrazine (2 g.), was purified *via* its picrate (dark violet needles, m. p. 187°, from methanol), and formed colourless needles, m. p. 133°, from light petroleum (Found: C, 89·2; H, 5·9. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%).

3 : 4-*Dihydro*-6′-*methylnaphtho*(1′ : 2′-1 : 2)*acridine*-5-*carboxylic Acid* (VIII).—A solution of isatin (0·8 g.), 1 : 2 : 3 : 4-tetrahydro-7-methyl-4-oxophenanthrene (1 g.), and potassium hydroxide (0·8 g., dissolved in 1 c.c. of water) in ethanol (10 c.c.) was refluxed for 12 hr. The product was poured in water, the neutral impurities were removed with benzene, and the aqueous layer was acidified with acetic acid. The *cinchoninic acid* (1·1 g.) formed yellow prisms, m. p. 323—324° (decomp. from 312°), from ethanol (Found: C, 81·3; H, 5·0. $C_{23}H_{17}O_2N$ requires C, 81·4; H, 5·0%).

Indolo(3′ : 2′-20 : 21)*friedelene* (IX; R = H).—A mixture of friedelin (0·7 g.; m. p. 257—258°) and phenylhydrazine (1 g.) was heated at 130° for 30 min.; the crude *phenylhydrazone* (which could not be prepared in ethanol) yielded on cyclisation a product crystallising from ethanol–benzene as colourless prisms (0·5 g.), m. p. 309—310°, giving a brown-violet colour in ethanolic picric acid (Found: C, 86·2; H, 10·5. $C_{36}H_{53}N$ requires C, 86·6; H, 10·6%). 1′-*Methylindolo*(3′ : 2′-20 : 21)*friedelene* (IX; R = Me), prepared from friedelin (0·7 g.) and *N*-methylphenylhydrazine (1 g.), formed colourless prisms, m. p. 217—218°, from ethanol (Found: C, 86·2; H, 10·5. $C_{37}H_{55}N$ requires C, 86·5; H, 10·7%).

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303. *Organic Fluorine Compounds. Part V.* Infrared Studies on Fluoropyruvic Acid and Related Compounds.*

By Ernst D. Bergmann, Abraham Kalmus, and Shraga Pinchas.

The infrared spectrum of fluoropyruvic acid and related compounds reveals that in the acid a hydrogen bond exists between the carbonyl and the carboxyl group, whilst in the corresponding 2 : 4-dinitrophenylhydrazones and semicarbazones hydrogen bonding can occur between the fluorine atom and either the carboxyl or the NH group.

The carbonyl absorption of pyruvic acid (capillary liquid layer) lies at 1723 cm.$^{-1}$.

In contradistinction to fluoropyruvic acid, its 2 : 4-dinitrophenylhydrazone and its semicarbazone show the infrared vibration of the C–F linkage, which usually [1] absorbs between 1010 and 1120 cm.$^{-1}$, at 991 and 978 cm.$^{-1}$, respectively. This observation (which has been mentioned briefly, but evidently not clearly enough,[2] by Mager and Blank [3]) invited a further study, especially in view of the unusual biological properties of the semicarbazone of fluoropyruvic acid.[4]

It appears reasonable to assume that the shift of the C–F band is due to hydrogen bonding which will tend to weaken the C–F linkage and, therefore, lower its characteristic frequency. The possibility of hydrogen bonding between a fluorine atom and a hydroxyl group has been suggested before.[5,6] In the present case, two types of hydrogen bonding are possible, involving the NH group or the carboxyl group, as indicated in (I) and (II),

[R = CO·NH$_2$ or C$_6$H$_3$(NO$_2$)$_2$]

respectively. In order to clarify this point, the infrared spectra of the 2 : 4-dinitrophenylhydrazone of methyl fluoropyruvate and of the *N*-methyl-2 : 4-dinitrophenylhydrazone of fluoropyruvic acid were measured. In the former, bands at 992 (medium) and 1052 cm.$^{-1}$ (strong) have been observed, probably corresponding to a hydrogen-bonded and to a " free " C–F linkage, respectively. The hydrogen bonding can only involve the NH of the phenylhydrazone grouping, but it appears that this bond is weak, perhaps because the *o*-nitro-group competes with the fluorine atom for the hydrogen bond. In the *N*-methyldinitrophenylhydrazone of fluoropyruvic acid, a single strong band at 973 cm.$^{-1}$ represents the hydrogen-bonded C–F frequency : in this case, only the carboxyl group [according to (II)] can supply the hydrogen. One can, therefore, conclude, that form (II) is more stable than (I), and that (I) only applies when no free carboxyl group is available.

The assignment of the frequency in the 973—992 cm.$^{-1}$ region to the stretching of the hydrogen-bonded C–F linkage is supported by the spectrum of pyruvic acid *N*-methyl-2 : 4-dinitrophenylhydrazone, which, like the dinitrophenylhydrazones of pyruvic acid and methyl pyruvate, shows no band in that region.

There remains one point to be discussed. Whilst in methyl fluoropyruvate the location of the C–F bond at 1046 cm.$^{-1}$ is normal (no hydrogen bonding possible), one would expect a shift of this peak in the case of fluoropyruvic acid. However, in this compound also the C–F bond has been found at 1035 cm.$^{-1}$ (Thomas [2] gives 1022 cm.$^{-1}$, but his measurements were carried out on a solution of the compound, whilst in the present investigation a solid capillary layer has been used). The absence of this shift is best ascribed to a structure in

* Part IV, *J.*, 1955, 2190.

[1] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[2] Thomas, *Nature*, 1955, **175**, 424.
[3] Mager and Blank, *ibid.*, 1954, **173**, 126.
[4] Mager and Avi-Dor, unpublished results.
[5] Wulf, Liddel, and Hendricks, *J. Amer. Chem. Soc.*, 1936, **58**, 228.
[6] Park, Brown, and Lacher, *ibid.*, 1953, **75**, 4753.

which the carboxyl group is hydrogen-bonded to the ketonic carbonyl-oxygen either in the same or in a second molecule (formation of a dimer), thus leaving the C–F bond unaffected.

The difference in the hydrogen-bonded C–F frequency in the dinitrophenylhydrazones of fluoropyruvic acid (991 cm.$^{-1}$) on one hand, and in fluoropyruvic acid semicarbazone (978 cm.$^{-1}$) and *N*-methyldinitrophenylhydrazone (972 cm.$^{-1}$) on the other, is somewhat unexpected, but any attempt to explain this difference would be speculative.

The dinitrophenylhydrazones and *N*-methyldinitrophenylhydrazones described in this paper are well-defined crystalline substances. No *syn-anti*-isomerism of the type described recently by various authors [7] has been observed. It should be pointed out that the formation of hydrogen-bonded rings of type (I) presupposes that the substituents at the azomethine-nitrogen atom and the carboxyl (or ester) group are *trans* to each other.

In connection with these experiments, the carbonyl frequency of fluoropyruvic acid (solid capillary layer, obtained by cooling a thin molten layer of the acid) was measured as an intense, broad band centred at about 1723 cm.$^{-1}$. This value is considerably lower than that reported for pyruvic acid (1745 cm.$^{-1}$),[8] but lies rather in the region expected when one recalls that the interaction of the two carbonyl groups should increase only by very little the usual [9] frequency of 1715 cm.$^{-1}$. A further study of the spectrum of pyruvic acid (very thin liquid layer) showed the band to be at 1728 $\pm$ 4 cm.$^{-1}$, in agreement with the above figure for fluoropyruvic acid and the value (1726 cm.$^{-1}$) for 11 : 12-diketosteroids.[10] The fluorine atom might have been expected to *raise* somewhat the carbonyl frequency, but it is perhaps difficult to predict accurately the effect of the interaction of the various polar linkages, especially if the molecule is dimeric (see above).

Experimental

Fluoropyruvic acid and its methyl ester were prepared according to Mager, Blank, and Bergmann.[11] The infrared spectrum of the ester was measured in CCl_4 solution (0·06 g. in 1 ml.; 0·1-mm. cell).

The 2 : 4-*dinitrophenylhydrazone* of the methyl ester was prepared by the standard procedure,[12] though the yield was low. It formed orange-yellow crystals and melted, after recrystallization from alcohol, at 245° (Found: C, 39·8; H, 3·0; N, 18·8. $C_{10}H_9O_6N_4F$ requires C, 40·0; H, 3·0; N, 18·7%). The infrared spectrum was measured in a paraffin oil mull; bands were observed at 992, 1052, 1077, and 1144 cm.$^{-1}$.

N-Methyl-2 : 4-dinitrophenylhydrazine was prepared according to Blanksma and Wackers,[13] from methylhydrazine [14] and chloro-2 : 4-dinitrobenzene. Recrystallized from ethyl alcohol, it melted at 141°.

Fluoropyruvic Acid N-Methyl-2 : 4-dinitrophenylhydrazone.—To a solution of the hydrazine derivative (1 g.) in 95% ethanol (50 ml.), a solution of fluoropyruvic acid (0·5 g.) in ethanol (10 ml.) and 2 drops of concentrated sulphuric acid were added. The mixture was refluxed for 10 min. and evaporated *in vacuo* until an oil separated. This was triturated with, and recrystallized from ethyl acetate; it formed yellow crystals, m. p. 158—159° (Found: C, 40·7; H, 3·2. $C_{10}H_9O_6N_4F$ requires C, 40·0; H, 3·0%). The ultraviolet spectrum showed a broad maximum at 380 mμ (log ε 3·74) (in EtOH). The infrared spectrum was measured on a mull in paraffin oil. The following bands were observed in the 900—1220 cm.$^{-1}$ region (the relative absorbances are given in parentheses): 909 (0·37), 973 (0·65), 1062 (0·43), 1112 (0·53), 1146 (0·50), 1175 (0·55).

Pyruvic Acid N-Methyl-2 : 4-dinitrophenylhydrazone.—The above method was applied to pyruvic acid. The *product* separated from butanol as yellow crystals, m. p. 164° (decomp.) (Found: C, 42·5; H, 3·6; N, 20·4. $C_{10}H_{10}O_6N_4$ requires C, 42·6; H, 3·6; N, 20·0%). Ultraviolet

[7] Stewart, *Biochem. J.*, 1953, **55**, 26; Isherwood and Cruickshank, *Nature*, 1954, **173**, 121; Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1954, **76**, 1037; van Duin, *Rec. Trav. chim.*, 1954, **73**, 78; Denny and Reid, *Chem. and Ind.*, 1954, 755; Khromov-Borisov, *Chem. Abstr.*, 1955, **49**, 8257.

[8] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," van Nostrand, New York, 1949, p. 104.

[9] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 122.

[10] Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1949, **71**, 241.

[11] Mager, Blank, and Bergmann, *J.*, 1955, 2190.

[12] Shriner and Fuson, "Identification of Organic Compounds," 3rd edn., Wiley, New York, 1948, p. 131.

[13] Blanksma and Wackers, *Rec. Trav. chim.*, 1936, **55**, 655.

[14] *Org. Synth.*, Coll. Vol. II, p. 395.

spectrum: $\lambda_{max.}$ 383 mμ (log ε 4·46) (in EtOH). Infrared spectrum, measured as in the preceding case: 919 (0·55), 941 (0·37), 1005 (0·72), 1038 (0·50; shoulder), 1061 (0·80), 1100 (0·55), 1141 (0·82), 1203 (0·98).

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304. *Organic Fluorine Compounds. Part VI.* The Enolates of Alkyl Fluoroacetates.*

By ERNST D. BERGMANN and S. SZINAI.

Treatment of ethyl fluoroacetate with sodium alkoxide or hydride gave an enolate which could be alkylated with benzyl bromide, *p*-bromobenzyl bromide, ethyl bromoacetate, and allyl bromide. Fluorosuccinic acid is too alkali-sensitive to be accessible by alkaline hydrolysis of its alkyl esters. The reaction with allyl bromide gave a saturated product, believed to be ethyl 1-fluoro*cyclo*butane-1-carboxylate.

ENOLATES of the esters of aliphatic acids are generally not stable; they are quickly transformed into the corresponding acetoacetates and are, therefore, not alkylated by alkyl halides or similar reagents. Analogously, when in certain Michael reactions products of the type $(RO_2C)_2CH{\cdot}CH_2{\cdot}CH{:}C(ONa){\cdot}OR'$ are formed, the course of their methylation is explained by the assumption that they rearrange to $RO{\cdot}C(ONa){:}C(CO_2R){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R$.[1,2] Even if, perhaps for steric reasons, stable enolates are formed, as, *e.g.*, from diethyl 3-methylbutane-2 : 3-dicarboxylate and triphenylmethylsodium, they do not appear to be very reactive.[3] Phenylacetates, on the other hand, give enolates which are both relatively stable and sufficiently responsive to alkylating agents.[4-10] The enolate of diphenylacetic acid has been isolated in crystalline form by Schlenk, Hillemann, and Rodloff,[11] and its alkylation reactions have been studied.[12,13] It appeared possible that negative substituents other than phenyl would have an analogous effect. Indeed, it has been found that ethyl fluoroacetate, when treated with sodium alkoxide or sodium hydride, gives an enolate which forms ethyl $\alpha\gamma$-difluoroacetoacetate sufficiently slowly to permit alkylation with reactive alkyl halides, such as benzyl or allyl bromide and ethyl bromoacetate. Normal alkyl halides fail to give significant amounts of alkylated fluoroacetates.

Benzyl bromide gave ethyl α-fluoro-β-phenylpropionic acid in 27 and 20% yield, respectively, when alcoholic sodium ethoxide or sodium hydride in ether was employed for the preparation of the enolate. Analysis and molecular refraction supported the formula of the ester, which could be converted into the corresponding acid and its amide without loss of the fluorine atom. Analogously, *p*-bromobenzyl bromide and sodium ethoxide led to a 20% yield of ethyl β-*p*-bromophenyl-2-fluoropropionate, from which the free acid and the amide have been prepared.

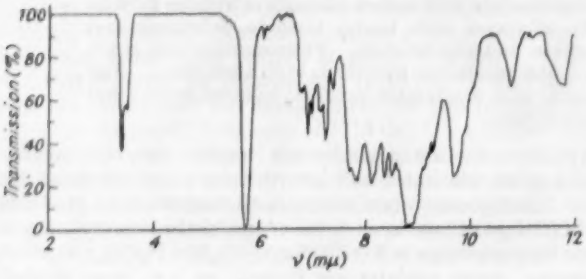
With ethyl bromoacetate, a 25·5% yield of diethyl fluorosuccinate was obtained which, however, lost fluorine even under mild conditions of alkaline hydrolysis. Also with aqueous ammonia only fumaramide was obtained. In an attempt to circumvent the alkaline hydrolysis of the fluorosuccinate, dibenzyl fluorosuccinate was prepared from the

* Part V, preceding paper.

[1] Thorpe, *J.*, 1900, **77**, 923.
[2] Ingold and Powell, *J.*, 1921, **119**, 1976.
[3] Talakdar and Bagchi, *J. Org. Chem.*, 1955, **20**, 13.
[4] Ramart and Haller, *Compt. rend.*, 1924, **178**, 1583.
[5] Scheibler, Marhenkel, and Bassanoff, *Ber.*, 1925, **58**, 1198.
[6] Snell and McElvain, *J. Amer. Chem. Soc.*, 1931, **53**, 750.
[7] Mueller, Gawlick, and Kreutzmann, *Annalen*, 1935, **515**, 97.
[8] Roberts and McElvain, *J. Amer. Chem. Soc.*, 1937, **59**, 2007.
[9] Hauser, *ibid.*, 1938, **60**, 1957.
[10] Hauser and Hudson, *ibid.*, 1940, **62**, 62.
[11] Schlenk, Hillemann, and Rodloff, *Annalen*, 1931, **487**, 135.
[12] Staudinger and Meyer, *Helv. Chim. Acta*, 1922, **5**, 656.
[13] Ramart, *Compt. rend.*, 1924, **178**, 93, **396**; *Bull. Soc. chim., France*, 1924, **35**, 196.

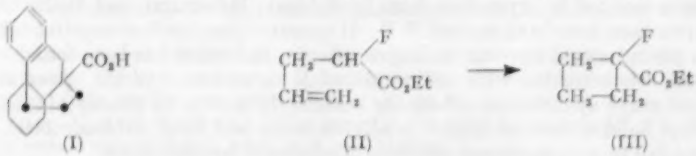
enolate of benzyl fluoroacetate and benzyl bromoacetate. The ester decomposed partly even upon distillation under 1·25 mm. pressure; upon hydrogenolysis, only fumaric acid could be isolated. A similar instability has been noted for αβ-difluorosuccinic acid which in contact with water gives acetylenedicarboxylic acid.[14]

The product isolated in 45% yield from allyl bromide, and the amide prepared from it, gave the correct analytical results for the expected ethyl 2-fluoropent-4-enoate and the derived amide; however, the ester was saturated towards bromine and catalytically activated hydrogen, and did not show the characteristic [15] infrared band for mono-substituted ethylenes at 1643 cm.$^{-1}$ (see Fig.). Also the C–H stretching frequencies in the 3010—3040 and 3075—3095 cm.$^{-1}$ regions and the C–H out-of-plane deformation frequency at 985—995 cm.$^{-1}$ were absent. As Grewe [16] has observed that 4*a*-allyl-



Infrared spectrum of ethyl 1-*fluoro-cyclobutane*-1-*carboxylate (in carbon tetrachloride solution).*

1 : 2 : 3 : 4 : 9 : 10 : 4*a* : 10*a*-octahydrophenanthrene-10-carboxylic acid isomerizes spontaneously to the compound (I), it is assumed that ethyl 2-fluoropent-4-enoate (II) isomerizes [17] spontaneously to ethyl 1-fluoro*cyclo*butane-1-carboxylate (III). The infrared



(I) (II) (III)

spectrum shows, indeed, a band at 927 cm.$^{-1}$, where a band typical of the *cyclo*butane ring is said to occur.[18] The C–F band at 1030 cm.$^{-1}$ has also been found; the ester-carbonyl frequency is situated at 1740 cm.$^{-1}$, whilst for ethyl fluoroacetate McBee and Christman [19] report a frequency of 1778 cm.$^{-1}$.

Analogous attempts to prepare and utilize the enolate of *tert.*-butyl instead of ethyl fluoroacetate failed. This enolate is formed only at high temperatures, at which the conversion into *tert.*-butyl αγ-difluoroacetoacetate is too rapid.

A convenient synthesis of *tert.*-butyl fluoroacetate from *iso*butene and fluoroacetic acid in the presence of concentrated sulphuric acid or boron trifluoride–ether complex is described.

Experimental

Ethyl α-Fluoro-β-phenylpropionate.—(*a*) A solution of ethyl fluoroacetate (53 g., 0·5 mole) in anhydrous alcohol (100 ml.) was added dropwise (30 min.) to a solution of sodium ethoxide [from sodium (11·5 g.) and anhydrous alcohol (200 ml.)]. After 1 hr. at room temperature, freshly distilled benzyl bromide (94 g., 0·55 mole) was added slowly (1 hr.) at 20° with vigorous agitation. The mixture was kept for 12 hr., filtered, and distilled through a short Vigreux

[14] Kharasch, U.S.P. 2,426,224; *Chem. Abs.*, 1948, **42**, 213.
[15] Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1.
[16] Grewe, *Ber.*, 1943, **76**, 1076.
[17] Vejdelek and Kakac, *Chem. Abs.*, 1955, **49**, 9565.
[18] Bellamy, "The Infra-red Spectra of Complex Molecules," pp. 28—29, Wiley, London and New York, 1954.
[19] McBee and Christman, *J. Amer. Chem. Soc.*, 1955, **77**, 755.

column, the fraction of b. p. 95—145°/20 mm. being collected. Fractionation of this distillate gave benzyl ethyl ether, b. p. 129—130°/20 mm. (50 g.), and *ethyl α-fluoro-β-phenylpropionate* (26 g., 27%), b. p. 136—137·5°/20 mm., $d_0^{14·5}$ 1·1211, $n_D^{14·5}$ 1·4890, $[R]_M$ 50·51 (Calc.: 50·75) (Found: C, 67·2; H, 6·8; F, 9·4. $C_{11}H_{13}O_2F$ requires C, 67·4; H, 6·7; F, 9·7%).

(*b*) Sodium hydride (12 g., 0·5 mole) was suspended under nitrogen in anhydrous ether (200 ml.), and at 0°, a solution of ethyl fluoroacetate (53 g., 0·5 mole) in ether (200 ml.) was added during 4 hr. (If evolution of hydrogen does not set in within 10 min., reaction is initiated by addition of two drops of anhydrous alcohol.) Stirring was continued for 4 hr. more, and anhydrous alcohol (50 ml.) and a solution of benzyl bromide (94 g.) in anhydrous ether (200 ml.) were added successively. After 21 hr. the mixture was poured into the theoretical quantity of 20% sulphuric acid, the organic layer separated, and the aqueous phase extracted twice with ether. The combined ethereal solutions were washed with 10% sodium hydrogen carbonate solution, dried, and distilled; the product (20 g., 20%) had b. p. 136—137·5°/20 mm.

α-Fluoro-β-phenylpropionic Acid.—The preceding ester (6·8 g.) was added to a solution of potassium hydroxide (2·8 g.) in anhydrous alcohol (20 ml.), and after 30 min., the precipitate was filtered off, washed with alcohol and ether (weight, 6·5 g.), and dissolved in water, and the solution acidified with hydrochloric acid and extracted with ether. Distillation (b. p. 103°/0·3 mm.; 155°/10 mm.) or recrystallisation from low-boiling light petroleum gave the pure *acid* (5·2 g., 90%), m. p. 73·2° (Found: C, 64·5; H, 5·7; F, 11·1. $C_9H_9O_2F$ requires C, 64·3; H, 5·4; F, 11·4%).

α-Fluoro-β-phenylpropionamide.—A mixture of the ethyl ester (2·0 g.) and concentrated aqueous ammonia (20 ml.) was stirred at 50—60° until homogeneous. On cooling, the *amide* crystallized. It was recrystallized twice from water and melted at 134° (yield, 1·0 g., 60%) (Found: C, 64·9; H, 6·3; F, 11·2. $C_9H_{10}ONF$ requires C, 64·7; H, 6·0; F, 11·4%).

Analogously, the following compounds were prepared from *p*-bromobenzyl bromide.[20] *Ethyl* β-p-*bromophenyl-α-fluoropropionate*, b. p. 102°/0·3 mm. (yield, 20%) d_4^{15} 1·4280, n_D^{15} 1·5230, $[R]_M$ 58·83 (Calc.: 58·71) (Found: C, 47·8; H, 4·8; Br, 28·8; F, 6·8. $C_{11}H_{12}O_2BrF$ requires C, 48·0; H, 4·4; Br, 29·1; F, 6·9%). β-p-*Bromophenyl-α-fluoropropionic acid*, from benzene, m. p. 159°, yield 83% (Found: C, 43·5; H, 3·2; Br, 32·6; F, 7·8. $C_9H_8O_2BrF$ requires C, 43·8; H, 3·3; Br, 32·4; F, 7·7%). β-p-*Bromophenyl-α-fluoropropionamide* (from water), m. p. 167°; yield, 52% (Found: C, 43·6; H, 3·4; N, 6·1; F, 7·8. C_9H_9ONBrF requires C, 43·9; H, 3·7; N, 5·7; F, 7·7%).

Diethyl Fluorosuccinate.—The enolate of ethyl fluoroacetate was prepared from sodium ethoxide as described above, and ethyl bromoacetate (91·8 g.; 0·5 mole) was added. Diethyl fluorosuccinate forms a liquid, b. p. 70—71°/0·8 mm., which could not be obtained pure; yield 24·5 g. (25·5%); n_D^{23} 1·4240, d_4^{23} 1·1090, $[R]_M$ 44·23 (Calc.: 42·34) (Found: C, 48·5; H, 6·5. Calc. for $C_8H_{13}O_4F$: C, 50·0; H, 6·7%). With sodium hydride as enolizing agent, a yield of 8 g. (8%), b. p. 68—72°/0·5 mm., was obtained.

Fumardiamide.—When diethyl fluorosuccinate was heated with aqueous ammonia at 50° for 0·5 hr., a crystalline product of m. p. 265—268° (decomp.) was obtained. By analysis and comparison with an authentic specimen[21] it was shown to be fumardiamide (Found: C, 42·2; H, 5·7; N, 25·6. Calc. for $C_4H_6O_2N_2$: C, 42·1; H, 5·3; N, 24·5%).

Benzyl Fluoroacetate.—A mixture of ethyl fluoroacetate (106 g.), benzyl alcohol (108 g.), and toluene-*p*-sulphonic acid (2 g.) was heated under a Fenske column, so that the ethanol formed distilled off continuously. After the desired amount of alcohol had been removed and the mixture cooled to room temperature, it was washed with 10% sodium carbonate solution and water and dried; the product (129 g.; 78%) had b. p. 137—141°/22 mm.

Benzyl Bromoacetate.—The same method was employed, but toluene (140 g. per mole) was added, in order to facilitate removal of the alcohol as azeotrope (90 ml.); the product (yield, 85%) had b. p. 166—170°/22 mm.

Dibenzyl Fluorosuccinate.—An ethereal solution of benzyl fluoroacetate (16·8 g.) was added dropwise to sodium hydride (2·4 g.) in refluxing ether. The mixture was stirred for 1 hr. at reflux temperature, and benzyl bromoacetate (22·9 g.) added dropwise. After 12 hr., the mixture was poured into ice-water, containing sulphuric acid (50 g.). After being repeatedly washed with 10% sodium carbonate solution and water and dried, the product was distilled at 1·25 mm. The distillation was accompanied by decomposition, and the last two fractions were strongly coloured. The last fraction, b. p. 160—190°/1·25 mm. (8 g.) after having been

[20] Weizmann and Patai, *ibid.*, 1946, **68**, 150.
[21] Hell and Poliakoff, *Ber.*, 1892, **25**, 640.

decolorised with Norite and redistilled (b. p. 165—170°/1 mm.), gave analytical results indicating that it consisted of impure dibenzyl fluorosuccinate.

Ethyl 1-*Fluorocyclobutane*-1-*carboxylate.*—From ethyl fluoroacetate (55 g.) and sodium ethoxide (11·5 g. of sodium) the enolate was prepared as above; it was treated with freshly distilled allyl bromide (66·5 g., 0·55 mole). Working-up gave the desired *ester* (III) (33 g., 45%), b. p. 75—76°/35 mm., $d_4^{14\cdot5}$ 1·0062, $n_D^{14\cdot5}$ 1·4090 (Found: C, 57·5; H, 7·8; F, 13·0. $C_7H_{11}O_2F$ requires C, 57·5; H, 7·6; F, 13·0%). When an attempt was made to hydrogenate this ester (544 mg.) in 96% alcohol (13 ml.) at 29°, using platinum oxide as catalyst, only 0·8 ml. of hydrogen was absorbed.

1-*Fluorocyclobutane*-1-*carboxyamide.*—A mixture of the foregoing ester (1·5 g.) and concentrated aqueous ammonia (10 ml.) was stirred at 80—90° until dissolution was complete. After 12 hr. at room temperature, the solution was repeatedly extracted with ether, and the ether residue recrystallized from low-boiling light petroleum; the product (0·85 g., 73%) had m. p. 70—71° (Found: C, 51·3; H, 7·2; N, 11·9; F, 16·0. C_5H_8ONF requires C, 51·3; H, 6·9; N, 12·0; F, 16·2%). In contradistinction with the ethyl ester, the *amide* slowly absorbed hydrogen, activated by platinum oxide. However, no stoicheiometric quantities of hydrogen were consumed even after 2·5 hr. (total absorption: 0·283 mole).

tert.-*Butyl Fluoroacetate.*—A mixture of fluoroacetic acid (78 g., 1 mole), *iso*butene (112 g., 2 mole), and concentrated sulphuric acid (3 ml.) or boron trifluoride–ether complex (3 ml.) was shaken for 2 hr. at room temperature. The slightly exothermic reaction was kept under control by immersing the bottle in ice-water from time to time. After 12 hr. at room temperature, the product was cooled to −15° and poured into a mixture of sodium hydroxide (70 g.), water (250 ml.), and ice (250 g.). The aqueous layer was extracted with ether, and the organic layer, combined with the extract, washed with 2N-sodium hydroxide solution and water, dried, and distilled twice; the ester (75%) had b. p. 42°/20 mm.

Analogously, *tert.*-butyl chloro- and bromo-acetate and ethyl *tert.*-butyl malonate can be prepared in good yield. As far as the use of concentrated sulphuric acid is concerned, the method is an adaptation of that of Fonken and Johnson [23] and of Johnson, McCloskay, and Dunnigan.[23]

The carbon and hydrogen determinations were carried out according to Bodenheimer and Goldstein,[24] the fluorine determinations according to Eger and Yarden.[25]

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TEL-AVIV, ISRAEL.

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[23] Fonken and Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 831.
[23] Johnson, McCloskay, and Dunnigan, *ibid.*, 1950, **72**, 514.
[24] Bodenheimer and Goldstein, *Bull. Res. Council Israel*, 1953, **3**, 53.
[25] Eger and Yarden, *ibid.*, 1954, **4**, 305; *Analyt. Chem.*, 1956, **28**, in the press.

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305. *Organic Fluorine Compounds. Part VII.* The Perkin and Similar Reactions with Fluoroacetic Acid.*

By ERNST D. BERGMANN and JOSÉ SCHWARCZ.

Fluoroacetic acid and its derivatives can be condensed with aromatic aldehydes in reactions of the Perkin type. α-Fluorocinnamic acid and its *p*-nitro-derivative, 1-fluoro-4-phenylbutadiene-1-carboxylic acid, and β-*o*-chlorophenyl-α-fluoro-β-hydroxypropionic acid have thus been synthesised; the yields are low. *m*-Nitrobenzaldehyde gives complicated products.

THE ability of fluoroacetates to form relatively stable enolates (see preceding paper) should express itself also in a tendency of the acid and its derivatives to condense with aromatic aldehydes to form compounds of the α-fluorocinnamic acid type. It is assumed today [1] that, *e.g.*, the Perkin reaction proceeds *via* the enolate of the acid anhydride used in the condensation. Indeed, Swarts [2] has reported that, from benzaldehyde, methyl fluoroacetate, and sodium, α-fluorocinnamic acid can be obtained (in unspecified yield), and

* Part VI, preceding paper.

[1] Gilman, "Organic Chemistry," Vol. III, p. 112, Wiley and Sons, New York, 1953.
[2] Swarts, *Bull. Soc. chim. France*, 1919, **25**, 325.

Bergmann, Kalmus, and Vromen [3] have described the alkaline condensation of benzaldehyde and ω-fluoroacetophenone in 40% yield. Ethyl bromofluoroacetate can also take part [4] in Reformatsky reactions. A systematic study of the condensation of aromatic aldehydes with fluoroacetic acid and its derivatives appeared, therefore, desirable.

In the condensation of benzaldehyde with sodium fluoroacetate and fluoroacetic anhydride, vigorous evolution of hydrogen fluoride took place, but α-fluorocinnamic acid could be isolated in a yield of only 2%. When benzaldehyde was condensed with ethyl fluoroacetate in ether in the presence of sodium hydride, a complex mixture was obtained: benzaldehyde, benzoic acid, ethyl benzoate, ethyl αγ-difluoroacetoacetate, cinnamic acid, and, in 15% yield, α-fluorocinnamic acid were isolated. (The mixture was treated with alcohol and hydrochloric acid to destroy the excess of sodium hydride; this may explain the formation of ethyl benzoate.) It is surprising that the product contains free acids, but even more so that, from the unidentified liquid fractions, we obtained a 2 : 4-dinitrophenylhydrazone which, according to the analysis and the ultraviolet spectrum (see below), was that of α-fluorocinnamaldehyde. Reduction has not been reported before in sodium hydride condensations.

The sodium hydride-catalysed condensation between cinnamaldehyde and ethyl fluoroacetate gave a mixture of 1-fluoro-4-phenylbuta-1 : 3-diene-1-carboxylic acid (14%) and its ethyl ester (20%). From *p*-nitrobenzaldehyde, a 13% yield of α-fluoro-*p*-nitrocinnamic acid was obtained by Perkin's method.

When *o*-chlorobenzaldehyde was condensed with ethyl fluoroacetate in the presence of sodium hydride, the reaction proceeded only to the stage of β-*o*-chlorophenyl-α-fluoro-β-hydroxypropionic acid, probably owing to the stabilising effect of a hydrogen bond between the hydroxyl group and the *o*-chlorine atom. Indeed, in the infrared spectrum of the acid, one finds in addition to the usual (3325 cm.$^{-1}$) band of the alcoholic hydroxyl, an intense absorption at 2560 cm.$^{-1}$, indicating a very strongly hydrogen-bonded aliphatic hydroxyl group; the carbonyl absorption lies at 1725 cm.$^{-1}$, *i.e.*, in the region characteristic of a saturated carboxylic acid.

The condensation of *m*-nitrobenzaldehyde with fluoroacetic acid under various conditions gave a number of abnormal products which will be reported later. In a Perkin-type condensation, for example, a compound $C_{16}H_{13}O_8N_2F$ was obtained, whose infrared spectrum suggests an *iso*butyric acid, $NO_2 \cdot C_6H_4 \cdot CH(OH) \cdot CF(CO_2H) \cdot CH(OH) \cdot C_6H_4 \cdot NO_2$.

Spectra.—Comparison of the spectra of α-fluorocinnamic acid and 1-fluoro-4-phenylbutadiene-1-carboxylic acid with those of the corresponding non-fluorinated compounds shows that the fluorine atom exerts a hypsochromic influence (−160 and −120 Å, respectively):

	Max. (Å)	Min. (Å)
α-Fluorocinnamic acid	2620 (log ε 4·36)	2260 (log ε 3·70)
Cinnamic acid [a]	2780	2350
1-Fluoro-4-phenylbutadiene-1-carboxylic acid	3020 (log ε 4·63)	2470 (log ε 3·64)
4-Phenylbutadiene-1-carboxylic acid [b]	3140	2500

[a] Landolt-Börnstein, "Physikalisch-chemische Tabellen," Vol. I, Part 3, p. 134. [b] Smakula, *Angew. Chem.*, 1934, **47**, 657; 1935, **48**, 152.

Equally, the 2 : 4-dinitrophenylhydrazone of our supposed α-fluorocinnamaldehyde shows maxima at 3710 (4·21) and 2500 Å (3·92) and minima at 3010 (3·37) and 2440 Å (3·89), whilst for cinnamaldehyde dinitrophenylhydrazone maxima at 3890 (4·68), 3040 (4·18), and 2365 Å (4·32) and minima at 3265 (3·95) and 2830 Å (4·04) are observed. Johnson [5] reports the longest maximum of cinnamaldehyde 2 : 4-dinitrophenylhydrazone at 3910 Å (4·59). The hypsochromic effect of the fluorine atom in this case is −180 Å (for the longest absorption band).

For α-fluoro-*p*-nitrocinnamic acid, the maxima lie at 2500 (4·03) and 3120 Å (4·17) and a minimum at 2630 Å (3·64). As Purvis [6] reported for *p*-nitrocinnamic acid an absorption maximum at 2940 Å, the fluorine atom would exert in this case a slightly bathochromic

[3] Bergmann, Kalmus, and Vromen, *J. Amer. Chem. Soc.*, 1955, **77**, 2494.
[4] McBee, Pierce, and Christman, *ibid.*, p. 1581.
[5] Johnson, *ibid.*, 1953, **75**, 2720.
[6] Purvis, *J.*, 1915, **107**, 966.

effect, as compared with the cinnamic acid, provided that the steric arrangement is the same as in α-fluorocinnamic acid. In this respect, it is recalled that α-fluorobenzylideneacetophenone has practically the same spectrum as the non-fluorinated compound.[3]

In the infrared spectrum,[7] the C:CF grouping absorbs at 1100—1200 cm.$^{-1}$, *i.e.*, in a region in which also many oxygenated compounds absorb and which, therefore, is not very convenient for the structural analysis of the compounds described here. In ethyl 1-fluoro-4-phenylbutadiene-1-carboxylate, the bands characteristic of the conjugated double bond and the conjugated ester grouping lie at **1643** and 1720 cm.$^{-1}$, respectively. The corresponding bands in the corresponding free acid and in α-fluoro-*p*-nitrocinnamic acid have been observed at **1639** and **1690** cm.$^{-1}$ and at **1606** and **1704** cm.$^{-1}$, respectively.[8,9] In the last compound, the C=CF band at **1124** cm.$^{-1}$ is very conspicuous.

Experimental

For the preparation of fluoroacetic acid and its anhydride the following modifications of known [10] methods have proved advantageous: Dry sodium fluoroacetate (50 g.) was added to concentrated sulphuric acid (100 ml.) in a Claisen flask. By gentle heating and stirring, a homogeneous solution was obtained. This was distilled *in vacuo*; the acid (37·1 g., 95%) on redistillation had b. p. **167—169°/760** mm.

Fluoroacetyl chloride [10] (38·7 g.) and sodium fluoroacetate (42·0 g.) were added to mineral oil (150 ml.) which had been freed from volatile constituents at 200°/30 mm. The mixture was heated under reflux at 110—120° for 90 min. and then distilled under 30—45 mm. pressure. The distillate was collected up to 116° and redistilled; the anhydride (44·4 g., 88%) had b. p. 90—93°/20 mm.

Condensation of Benzaldehyde and Fluoroacetic Acid.—(*a*) The mixture of freshly distilled benzaldehyde (16 g.), dry sodium fluoroacetate (15 g.), and fluoroacetic anhydride (20·7 g.) was heated under reflux for 8 hr. The product was steam-distilled; from the remaining aqueous liquor, α-fluorocinnamic acid (1·0 g., 2%) slowly crystallised. After being sublimed *in vacuo*, it melted at 157° (lit., 157·6°) (Found: C, 64·6; H, 4·3. Calc. for $C_9H_7O_2F$: C, 65·0; H, 4·2%).

(*b*) To sodium hydride (7·2 g., 0·3 mole) and anhydrous ether (65 ml.), contained under nitrogen, a solution of benzaldehyde (31·0 g., 0·3 mole) and ethyl fluoroacetate [11] (31·8 g., 0·3 mole) in anhydrous ether (100 ml.) was added slowly with stirring; stirring was continued for 8 hr. Anhydrous alcohol (14 ml., 0·3 mole) was added cautiously, followed by 20% hydrochloric acid. The aqueous layer was extracted with ether, and the combined ethereal solutions were extracted with 10% sodium hydrogen carbonate solution, dried, and concentrated. Distillation of the residue gave some benzaldehyde, ethyl benzoate (6·5 g.), ethyl αγ-difluoroacetoacetate (8·2 g., b. p. 99—101°/20 mm.), and a higher-boiling mixture from which by the usual procedure *α-fluorocinnamaldehyde* 2:4-*dinitrophenylhydrazone* (0·6 g.) was obtained. This melted, after recrystallisation from ethyl acetate–ethanol, at 200—203° (Found: C, 54·6; H, 3·8. $C_{15}H_{11}O_4N_4F$ requires C, 54·5; H, 3·4%). The sodium carbonate extract, upon acidification, gave α-fluorocinnamic acid (7·5 g., 15%), m. p. 157°, after a little benzoic and cinnamic acid had been removed by sublimation *in vacuo*.

Cinnamaldehyde and Ethyl Fluoroacetate.—By the method described above, freshly distilled cinnamaldehyde (19·8 g.) was condensed with ethyl fluoroacetate (15·9 g.) in the presence of sodium hydride (3·6 g.). The mixture was refluxed with stirring for 10 hr. and decomposed with the equivalent amount (0·15 mole) of aqueous hydrochloric acid. The acidic product, *1-fluoro-4-phenylbutadiene-1-carboxylic acid*, was twice sublimed at 2 mm. at 140° and formed crystals (4 g., 14%), m. p. **192·5—193°** (Found: C, 69·1; H, 4·8; F, 9·8. $C_{11}H_9O_2F$ requires C, 68·7; H, 4·7; F, 9·9%). The neutral fraction was redistilled at 119°/0·75 mm.; it crystallised and melted at 40—42°. *Ethyl 1-fluoro-4-phenylbutadiene-1-carboxylate* decomposes gradually (Found: C, 71·2; H, 6·0%; *M*, 190. $C_{13}H_{13}O_2F$ requires C, 70·9; H, 5·9%; *M*, 220). Hydrolysis gave the free acid.

α-*Fluoro*-p-*nitrocinnamic Acid.*—The mixture of *p*-nitrobenzaldehyde (5·0 g.), sodium fluoroacetate (4·5 g.), and fluoroacetic anhydride (9·4 g.) was heated at 145° for 13 hr. The desired *acid* was isolated by extraction with aqueous ammonia and acidification of the extract.

[7] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[8] Dauben and Hance, *J. Amer. Chem. Soc.*, 1953, **75**, 3352.
[9] Grove and Willis, *J.*, 1951, 877.
[10] Saunders and Stacey, *J.*, 1948, 1773.
[11] Bergmann and Blank, *J.*, 1953, 3786.

The yellowish product was purified by sublimation (170°/0·9 mm.) and then had m. p. 200—202° (yield 0·9 g., 13%). The carbon analysis was somewhat low (Found: C, 50·5; H, 3·0; N, 6·7; F, 9·5. $C_9H_6O_4NF$ requires C, 51·2; H, 2·8; N, 6·6; F, 9·0%).

β-*o*-*Chlorophenyl*-α-*fluoro*-β-*hydroxypropionic Acid*.—In the manner described above, *o*-chlorobenzaldehyde (21·0 g.) and ethyl fluoroacetate (15·9 g.) were condensed in the presence of sodium hydride (3·6 g.). The resulting *acid* was successively recrystallised from water and benzene and formed platelets (yield 4·8 g., 15%), m. p. 136° (Found: Cl, 16·2; F, 8·7. $C_9H_8O_3ClF$ requires Cl, 16·1; F, 8·7%).

2-*Fluoro*-1 : 3-*dihydroxy*-1 : 3-*di*-m-*nitrophenylpropane*-2-*carboxylic Acid*.—The Perkin condensation of fluoroacetic acid and *m*-nitrobenzaldehyde was carried out as described for the *p*-isomer. The *acid* (yield 2·1 g., 33%) was purified by sublimation (155°/0·9 mm.) and melted at 174—176° (Found: C, 49·2; H, 3·2; N, 7·3; F, 5·0. $C_{16}H_{12}O_8N_2F$ requires C, 50·5; H, 3·4; N, 7·4; F, 4·8%).

Infrared Spectra.—These were determined on suspensions in Nujol, except for ethyl 1-fluoro-4-phenylbutadiene-1-carboxylate whose spectrum was measured in chloroform (0·0414 g. in 1 ml.).

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306. *Addition Compounds of Gallium Trichloride. Part I. A Comparison of the Binary Systems which Acyl Chlorides form with Boron and Gallium Trichlorides.*

By N. N. Greenwood and K. Wade.

The existence of the molecular addition compound boron trichloride–acetyl chloride (m. p. −54°) has been established by phase studies, but there is no evidence for a compound between boron trichloride and benzoyl chloride. Vapour pressures for the two systems at 0° show positive deviations from ideality, indicating that boron trichloride–acetyl chloride is stable only in the solid phase. Neither system shows Friedel–Crafts activity. By contrast, gallium trichloride forms compounds with both ligands (gallium trichloride–acetyl chloride, m. p. 86°, and gallium trichloride–benzoyl chloride, m. p. 46·5°), and these complexes are powerful Friedel–Crafts acylating agents. The electrical conductivity of gallium trichloride–benzoyl chloride suggests that the compound is appreciably ionized in the molten state, whereas the system involving boron trichloride and benzoyl chloride is virtually non-conducting.

The vapour pressures and heats of vaporization of highly purified boron trichloride and acetyl chloride, and the m. p. of vacuum-sublimed gallium trichloride, have been redetermined.

Gallium trichloride is known to co-ordinate to ammonia,[1] trimethylamine,[2] and benzonitrile,[3] as well as to dimethyl ether [2] and *p*-nitrotoluene.[3] In all other systems the ligand contains a halogen atom, usually chlorine, and this is presumably the donor atom.[4-7] Hydrogen chloride also forms complexes providing that a subsidiary ligand such as ammonia,[4] toluene,[5] mesitylene,[5] or an ether [8,9] is present to stabilise the proton. In all these complexes, especially those in which chlorine is the donor, gallium trichloride shows a marked resemblance to aluminium trichloride. By contrast, boron trichloride co-ordinates to several of the elements in Groups V and VI, but forms few stable complexes

[1] Klemm, Tilk, and Jacobi, *Z. anorg. Chem.*, 1932, **207**, 187.
[2] Van Dyke and Crawford, *J. Amer. Chem. Soc.*, 1950, **72**, 2829.
[3] Ulich and Heyne, *Z. phys. Chem.*, 1941, **49**, *B*, 284.
[4] Friedman and Taube, *J. Amer. Chem. Soc.*, 1950, **72**, 2236.
[5] Brown, Pearsall, and Eddy, *ibid.*, p. 5347.
[6] Brown, Eddy, and Wong, *ibid.*, 1953, **75**, 6275.
[7] Partington and Whynes, *J.*, 1948, 1952.
[8] Wiberg, Schmidt, and Galinos, *Angew. Chem.*, 1954, **66**, 442.
[9] Nachtrieb and Fryxell, *J. Amer. Chem. Soc.*, 1949, **71**, 4035.

with ligands in which chlorine is the donor atom.[10] The alkali-metal chlorides do not react to give compounds analogous to the tetrachlorogallates;[11] there are no complexes in the systems with methyl or *n*-propyl chloride, and, even when compounds are observed, as with ethyl and *iso*propyl chloride, they do not occur at the 1 : 1 ratio and melt at extraordinarily low temperatures.[12, 13]

In order to establish more clearly the reason for this difference in behaviour between boron trichloride on the one hand and aluminium and gallium trichlorides on the other, the binary systems of boron trichloride and gallium trichloride with acetyl chloride and benzoyl chloride were studied. The properties of the compounds formed between aluminium trichloride and these acyl halides are well known [14-19] and were not further investigated. A solid phase of composition BCl_3,AcCl has been reported previously,[20] and some properties of the compound gallium trichloride–benzoyl chloride are known.[3, 21, 22] These results will be referred to later.

Experimental

Materials.—Commercial boron trichloride was purified by fractional distillation in a vacuum-line between −50° (36 mm. pressure) and −78° (5 mm. pressure). Successive fractions of the purified compound gave identical vapour pressures at a series of temperatures between −78° and 0° and these values also agreed, within the experimental error of 1 mm., with those given by Stock and Priess.[23] The m. p. was −107°.

Gallium trichloride was prepared from high-purity gallium metal (Messrs. Johnson Matthey and Co. Ltd.) by heating 28 g. in a current of dry chlorine in an all-glass apparatus similar to that described for the preparation of tellurium tetrachloride.[24] The product, which was a very pale pink,[25] was sealed in tubes under chlorine and then purified by distillation in chlorine, followed by two vacuum-sublimations at 80° in an apparatus[25] based on that described by T. W. Richards. First and last fractions were discarded and a final sublimate, from a bath held at 75°, was collected and sealed in ten receivers. The product formed large, colourless, brilliantly transparent crystals and each of the ten samples had a sharp m. p. within the range 77·75° ± 0·05°. This compares favourably with published values of 77·65°,[26] 77·0°,[27] 77·9° ± 0·2°,[28] and 78·0° ± 0·3°.[29]

Acetyl chloride was fractionated at 762 mm. through a 50 cm. column packed with glass helices, and the fraction boiling at 51·6—51·7° was collected at a take-off ratio of 1 : 70. This was further purified in the vacuum-line by distillation at −15° (37 mm. pressure) until a tensiometrically homogeneous product was obtained; this had m. p. −98°.

Benzoyl chloride was fractionated at 8 mm. in the column described above and the fraction boiling at 70·0° was collected at a take-off ratio of 1 : 50. The m. p. was −0·5°.

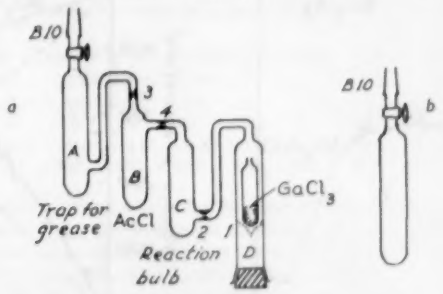
Transfer of Reactants.—Unless otherwise stated, all compounds were transferred in a vacuum-line which was flamed before use. Preliminary experiments showed that boron trichloride reacted rapidly with Silicone grease, to give a gas which was not condensed at −78°, and a liquid of b. p. approx. 100°. Apiezon greases M and L were both satisfactory, but Apiezon M was considered the better. These greases darkened only slightly in the presence of the trichlorides alone but there was some attack when acetyl chloride was also present.

[10] Martin, *Chem. Rev.*, 1944, **34**, 461.
[11] Unpublished observations in this Laboratory.
[12] Martin and Hicks, *J. Phys. Chem.*, 1946, **50**, 422.
[13] Martin and Humphrey, *ibid.*, 1947, **51**, 425.
[14] Perrier, *Compt. rend.*, 1893, **116**, 1298.
[15] Boeseken, *Rec. Trav. chim.*, 1900, **19**, 21.
[16] Ulich, *ibid.*, 1901, **20**, 102.
[17] Menschutkin, *J. Russ. phys.-chem. Ges.*, 1910, **42**, 1310, *Chem. Zentr.*, 1911, I, 481.
[18] *Idem*, *Z. phys. Chem.*, Bodenstein Festband, 1931, p. 423.
[19] Nespital, *Z. phys. Chem.*, 1932, **16**, *B*, 153.
[20] Meerwein and Maier-Hüser, *J. prakt. Chem.*, 1932, **51**, 134.
[21] Ulich, *Die Chemie*, 1942, **55**, 37.
[22] *Idem*, *Oel u. Kohle*, 1943, **39**, 523.
[23] Stock and Priess, *Ber.*, 1914, **47**, 3109.
[24] Suttle and Smith, *Inorg. Synth.*, **3**, 140.
[25] Richards and Craig, *J. Amer. Chem. Soc.*, 1923, **45**, 1155.
[26] Craig and Drake, *ibid.*, 1934, **56**, 584.
[27] Laubengayer and Schirmer, *ibid.*, 1940, **62**, 1578.
[28] Fischer and Jübermann, *Z. anorg. Chem.*, 1936, **227**, 227.
[29] Klemm and Tilk, *ibid.*, 1932, **207**, 161.

The design of reaction vessels used for particular experiments depended on the volatility of the reactants, but the method used to prepare mixtures of gallium trichloride and acetyl chloride for m. p. determinations may be described, as typical. The apparatus (Fig. 1*a*) was flamed under vacuum and then filled with dry air. A sample tube of gallium trichloride was weakened by a file mark, weighed, broken cleanly, and placed in limb *D* which was then sealed at point 1. The apparatus was evacuated and the gallium trichloride was sublimed at 80° into limb *C* which was then sealed at 2. Tube *D* was broken open, the two halves of the sample tube were weighed, and the weight of gallium trichloride was calculated by difference. The required amount of acetyl chloride was vacuum-distilled from a bulb held at −15° into a weighing tube (Fig. 1*b*), after which it was distilled at low pressure into limb *B* which was then sealed at 3. As the acetyl chloride warmed to room temperature, its vapour was rapidly absorbed by the solid gallium trichloride in *C* with considerable evolution of heat. The transfer was completed by cooling *C* which was finally sealed at 4.

A semimicro-burette graduated in 0·01 ml. was used in the preparation of mixtures of gallium trichloride and benzoyl chloride, as both components were involatile at room temperature. The benzoyl chloride, in a burette protected by means of a phosphoric oxide guard-tube, was run on to gallium trichloride in a B14 test-tube with a side-arm which also carried a phosphoric oxide tube. Silicone grease was found to be the most suitable lubricant for the burette tap. The m. p. was determined after each addition without dismantling the apparatus.

FIG. 1.



Physical Measurements.—Temperatures above −20° were read on an accurate mercury thermometer; below −20° an alcohol-in-glass thermometer which had been calibrated against a platinum resistance thermometer was used. Corrections for emergent stem were applied. In some instances (*e.g.*, boron trichloride–benzoyl chloride) it was possible to immerse the thermometer in the mixture and plot warming curves. When sealed tubes were used, the sample was heated very slowly (less than 1° in 5 min.) in a bath, the temperature of disappearance of the solid phase being taken as the m. p.

Vapour pressures were read directly on mercury manometers. In some systems >1 hr. was required for vapour-pressure equilibration, but for the pure components equilibrium was attained after a few minutes. Low temperatures were maintained by the addition of pellets of solid carbon dioxide to a stirred bath of alcohol in a Dewar flask.

Electrical conductivities in the system boron trichloride–benzoyl chloride were measured at 1000 cycles a.c. by means of a circuit and cell similar to those already described.[20, 21] The cell constant was 4·146 cm.$^{-1}$. The conductivity of the pure compound gallium trichloride–benzoyl chloride was measured with dipping electrodes in a cell of constant 0·377 cm.$^{-1}$.

RESULTS

System Boron Trichloride–Acetyl Chloride.—A partial phase diagram in the range 28—69% acetyl chloride was obtained by condensing the components from a vacuum-line into a reaction bulb at −78° and then allowing the white, crystalline product to warm slowly. The results of several experiments are presented in Table 1 and Fig. 2. The m. p. curve has a broad maximum at 50 mole % and there is no evidence of other compounds at either the 1 : 2 or the 2 : 1 ratio. The m. p. of the compound boron trichloride–acetyl chloride (−54°) is considerably above the

[20] Greenwood, Martin, and Emeléus, *J.*, 1950, 3030.
[21] *Idem*, *J.*, 1951, 1328.

m. p.s found for the pure components (BCl_3 −107°, AcCl −98°) and may be compared with the value of −60° to −70° given by Meerwein and Maier-Hüser for the equimolar mixture.[20]

Vapour-pressure measurements at 0° over the whole composition range (Table 2) show

TABLE 1. *Melting point of the system, boron trichloride–acetyl chloride.*

AcCl (mole %)	0·0	27·8	32·5	36·9	43·3	44·3	48·6	50·0	66·1	66·5	69·0	100·0
M. p.	−107°	−58°	−57°	−55·5°	−55°	−55°	−55°	−54°	−56°	−57°	−58°	−98°

TABLE 2. *Vapour pressure of the system boron trichloride–acetyl chloride at 0°*

AcCl (mole %)	0·0	5·2	10·8	16·7	28·6	36·2	40·7	48·6	52·7
Pressure (mm. Hg)...	478	473	460	456	434	415	396	394	376
AcCl (mole %)	59·3	65·3	68·9	77·1	81·4	89·7	93·1	100·0	
Pressure (mm. Hg)...	371	341	314	289	242	210	175	86	

positive deviations from Raoult's law (Fig. 3). This unexpected result suggests that the addition compound exists only in the solid phase and that its m. p. is, in effect, the temperature

FIG. 2. *M.p.s of systems with* BCl_3.

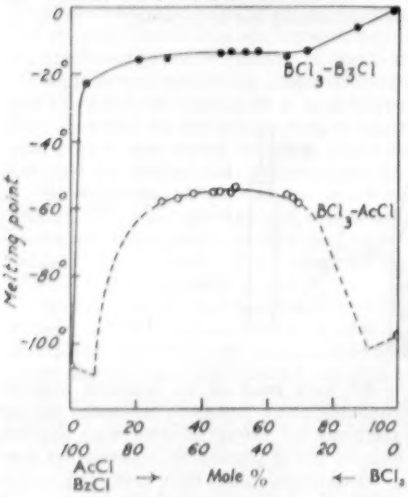
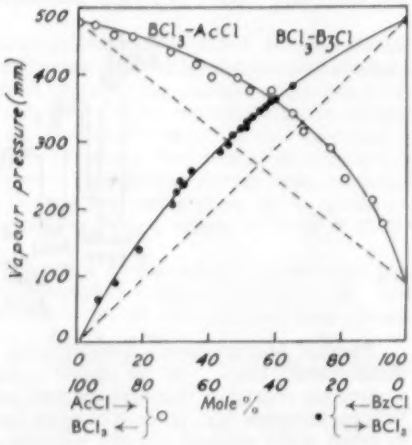


FIG. 3. *Vapour pressures of systems with* BCl_3 *at 0°.*



at which it dissociates into its components. That this dissociation is reversible is shown by the reproducibility of both melting point and vapour pressure throughout several thermal cycles.

Absence of association or compound-formation in the liquid phase was further indicated by the fact that the heat of vaporization of the equimolar mixture was less than that of either component, so that vaporization of the mixture could clearly not also involve the concurrent dissociation of a chemical bond. Thus, the vapour-pressure measurements by Stock and Priess on boron trichloride [21] imply a heat of vaporization of 6·28 kcal. $mole^{-1}$ at 0° and this value was confirmed by the present work in which vapour pressures between −78° and 0° were related to the absolute temperature by the equation,

$$\log p \text{ (mm.)} = 7{\cdot}700 - 1372/T$$

This equation represents the pressures to within ±1 mm. and by extrapolation gives b. p. 11·5°. The only determination of the vapour pressure of acetyl chloride over a range of temperatures appears to be that of Kireev and Popov [22] who express their results by the equation

$$\log p \text{ (mm.)} = 17{\cdot}16999 - 0{\cdot}023636T + 1{\cdot}75 \log T - 3570{\cdot}87/T$$

This implies that the heat of vaporization varies from 10·29 to 6·16 kcal. $mole^{-1}$ in the range −20° to +50° and is 9·22 kcal. $mole^{-1}$ at 0°. As these figures differ from the value of 6·84 kcal.

[22] Kireev and Popov, *J. Gen. Chem.* (*U.S.S.R.*), 1935, **5**, 1399.

mole^{-1} obtained directly at the b. p.,[23] the vapour pressure of acetyl chloride was redetermined between $-40°$ and $+20°$. The results are given in Table 3; above $-20°$ they may be represented to within ± 1 mm. by the equation

$$\log p \text{ (mm.)} = 8{\cdot}094 - 1684/T$$

This leads to a heat of vaporization of 7·68 kcal. mole^{-1} at 0° and an extrapolated b. p. of 49·9°.

The temperature dependence of the vapour pressure of a mixture containing 1·000 mol. of

TABLE 3. *Vapour pressure of acetyl chloride between −40° and +20°.*

Temp.	−37°	−28°	−21·0°	−19·0°	−16·7°	−13·8°	−10·8°	−8·3°	−6·5°	−3·5°
Pressure (mm.)	8	15	26	29	34	40	48	55	61	72
Temp.	−2·0°	−0·4°	0·0°	2·2°	4·7°	7·3°	12·4°	15·5°	17·6°	
Pressure (mm.)	77	84	86	96	111	124	159	183	200	

boron trichloride and 1·001 mol. of acetyl chloride was measured between −70° (supercooled) and +15°. The results, which are given in Table 4, may be represented by the following equation which is valid above −30°; at lower temperatures the measured pressures fall somewhat below this curve:

$$\log p \text{ (mm.)} = 7{\cdot}294 - 1294/T$$

The heat of vaporization at 0° is 5·92 kcal. mole^{-1} which is lower than the heat of vaporization of either component and is consistent with the positive deviation from ideality.

TABLE 4. *Vapour pressure of an equimolar mixture of boron trichloride and acetyl chloride between −70° and +15°.*

Temp.	−72°	−68°	−59°	−54°	−49°	−43°	−38°	−35°	−31°	−24°	−20·5°	−17·5°
Pressure (mm.)	8	9	16	23	29	42	55	66	86	132	150	174
Temp.	−13·0°	−8·5°	−6·0°	−3·5°	−0·5°	+1·5°	+3·0°	+6·5°	+8·0°	+10·7°	+13·4°	
Pressure (mm.)	217	261	287	322	359	391	420	473	500	552	604	

The Friedel–Crafts activity of an equimolar mixture of boron trichloride and acetyl chloride was investigated by treating the mixture with an excess of pure, sodium-dried benzene for 5 days at room temperature and then refluxing it for a further 3 hr. The product was worked up in the usual way but no trace of acetophenone was obtained.

The phase diagram, vapour-pressure curves, and catalysis experiment indicate that, whereas boron trichloride and acetyl chloride form a well-defined solid addition compound, there is no evidence for compound formation in the liquid or vapour phase.

System Boron Trichloride–Benzoyl Chloride.—When successive amounts of boron trichloride were condensed from the vacuum-line on to a weighed quantity of benzoyl chloride, the liquid, originally colourless, changed through pale yellow to deep green. However, experiments on separate samples showed that this gradual darkening of colour had no significant effect on the m. p. The m. p. was obtained for each composition from warming curves measured in triplicate. The data, given in Table 5 and plotted in Fig. 2, show no evidence of compound formation; there is a broad plateau at −13·8° between 30 and 70 mole %, but no maximum.

TABLE 5. *Melting point of the system boron trichloride–benzoyl chloride.*

BzCl (mole %)	0·0	4·8	20·4	28·9	45·3	48·1	52·9
M. p.	−107°	−22·8°	−15·8°	−14·8°	−13·8°	−13·6°	−13·7°
BzCl (mole %)	56·2	65·5	71·7	87·1	98·3	100	
M. p.	−13·3°	−14·5°	−12·8°	−5·8°	−0·5°	−0·5°	

TABLE 6. *Vapour pressure of the system boron trichloride–benzoyl chloride at 0°.*

BzCl (mole %)	0·0	34·3	35·4	39·6	41·1	42·8	44·6	46·5	48·2	48·5	50·5	52·7
Pressure (mm.)	478	380	378	361	358	351	344	336	324	328	319	308
BzCl (mole %)	53·9	56·2	65·4	68·1	68·3	70·0	70·9	81·4	88·3	93·6	100·0	
Pressure (mm.)	295	285	254	238	240	223	207	139	92	64	0·1	

The vapour-pressure measurements on the system boron trichloride–benzoyl chloride are summarized in Table 6. Fig. 3 shows that these values correspond to a positive deviation from ideality very similar to that obtained in the system of boron trichloride with acetyl chloride.

[23] Mathews and Fehlandt, *J. Amer. Chem. Soc.*, 1931, **53**, 3212.

The electrical conductivity of the system confirmed that there was but little interaction between the components. The conductivity of pure benzoyl chloride was below the limit of detectability of the apparatus used (5×10^{-7} ohm^{-1} cm.$^{-1}$); addition of boron trichloride increased the conductivity to about 10^{-6} ohm^{-1} cm.$^{-1}$, but variation of the concentration of boron trichloride from 17·8 to 29·4 mole % left the conductivity unaffected to within 1 part in 200.

Friedel–Crafts activity was not to be expected in such a system and an experiment with benzene, parallel to the one described for the boron trichloride–acetyl chloride system, gave negative results. When undried, commercial toluene was substituted for the purified benzene, a trace of 4-methylbenzophenone (m. p. 58°; 2 : 4-dinitrophenylhydrazone, m. p. 190°) was obtained after 10 weeks under pressure.

System Gallium Trichloride–Acetyl Chloride.—The phase diagram of the system gallium trichloride–acetyl chloride was difficult to obtain because melting was always accompanied by decomposition and chemical reaction (as distinct from reversible dissociation observed in the system with boron trichloride). This necessitated the preparation of separate mixtures for

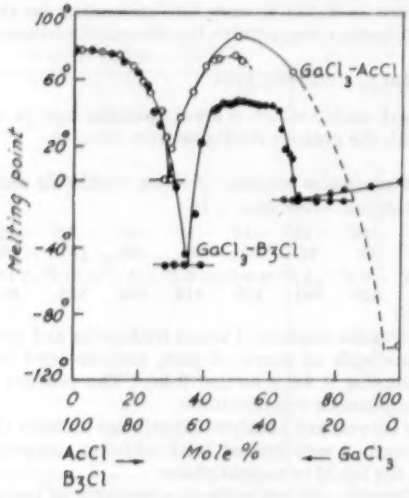


FIG. 4. *M.p.s of systems with* $GaCl_3$.

each m. p. determination by the rather tedious procedure outlined in the Experimental section. If, instead, successive amounts of acetyl chloride were condensed on to a given mixture which had previously been melted, then the m. p.s always fell below the true values characteristic of an unmelted mixture of the two components. A typical example is shown by the small dotted curve in Fig. 4, which refers to five successive additions of acetyl chloride to a mixture originally containing 36 mole %. It is seen that the full curve, obtained on samples individually prepared and melted only once, gives a maximum at the 1 : 1 ratio which is 12° higher than that of the sample which had been remelted several times. Similarly, the effect of repeated fusion on the m. p. of a given mixture at constant composition may be illustrated by the results on the pure 1 : 1 addition compound itself. This melts, with evolution of gas, at 86° (see Table 7), but

TABLE 7. *Melting point of the system gallium trichloride–acetyl chloride.*

AcCl (mole %)	0·0	2·1	8·3	13·9	18·0	21·2	23·2	26·5
M. p.	77·8°	77·6°	76·5°	75°	68°	59°	53°	40°
AcCl (mole %)	28·0	29·4	32·6	36·2	40·4	50·0	66·7	100·0
M. p.	25° *	19° *	37°	53°	68°	86°	65°	−98°

* And a eutectic at ~0°.

does not solidify completely when cooled to room temperature. On being reheated, the compound melted at 75° and after a further thermal cycle the m. p. was 60°. Under such conditions the measurement of vapour pressure has little significance, but it was established that the vapour pressure of the solid 1 : 1 compound at 20° was 6 mm. when freshly prepared (cf. acetyl chloride 222 mm.).

The compound gallium trichloride–acetyl chloride is an excellent acetylating agent. The complex (1·3 g.) was refluxed for 3 hr. with 6 ml. of pure, dry benzene under a phosphoric oxide guard-tube. The product, when washed with dilute alkali and water and then dried ($CaCl_2$), gave a 32% yield of acetophenone based on the acetyl chloride used (acetophenone, m. p. 19°; 2 : 4-dinitrophenylhydrazone, m. p. 235°, mixed m. p. 236°; semicarbazone, m. p. and mixed m. p. 198°).

System Gallium Trichloride–Benzoyl Chloride.—The existence of the compound gallium trichloride–benzoyl chloride was established by the m. p. data presented in Table 8 and Fig. 4.

TABLE 8. *Melting point of the system gallium trichloride–benzoyl chloride.*

BzCl (mole %)	0·0	5·4	11·7	15·3	19·2	22·2	24·4	26·0	28·0 *	31·3 *
M. p.	77·8°	77°	75°	71°	65°	57°	41°	33°	25°	−5°
BzCl (mole %)	33·9 *	36·7	38·9 *	42·6	43·8	45·8	47·4	49·0	49·7	50·4
M. p.	−44°	−20°	~22°	~41°	~42°	46°	46°	46·5°	46·5°	46·5°
BzCl (mole %)	51·8	53·3	54·7	56·4	58·4	60·3	62·0	63·1	64·3	65·8
M. p.	46·5°	46°	45·5°	45°	44·5°	44°	42°	30°	~18°	~15°
BzCl (mole %)	66·5	66·9 †	68·1 †	74·1 †	78·3 †	84·4 †	90·2	100·0		
M. p.	~13°	0°	−10°	−10°	−8°	−6°	−4°	−0·5°		

* And a eutectic at −50°. † And a eutectic at −12°.

The pure compound melts at 46·5°, presumably with some dissociation as 5 mole % excess of either component lowers the m. p. by only 1°. There are eutectics at 34 mole % of benzoyl chloride (−50°) and at 68 mole % (−12°). These results confirm and extend the observations of Ulich and Heyne [3] who found that an addition compound of m. p. 46° was precipitated by mixing solutions of the components in carbon tetrachloride. Fig. 3 also shows a slight irregularity at 64 mole % benzoyl chloride which might suggest an incongruently melting compound $GaCl_3,2BzCl$, but in this region supercooling and the viscous nature of the mixture make accurate observations difficult and the effect is probably within the experimental error. Moreover, the constancy of the eutectic temperature between 64 and 84 mole % of benzoyl chloride seems to preclude the existence of a second compound in this region, and the diagram may be taken as establishing only the equimolar addition compound unambiguously. As with the system gallium trichloride–acetyl chloride, the mixtures tended to discolour through pale straw to green, but melting was not accompanied by comparable decomposition and there was no evolution of gas during fusion.

The addition compound was shown to be ionic in the molten state by a preliminary measurement of its electrical conductivity, which gave a value of $1·08 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ at the m. p. This is greater than the conductivity of molten gallium trichloride [29] by a factor of more than 10^6 and is also well above the conductivity of benzoyl chloride which has been shown to be certainly less than 5×10^{-7} ohm^{-1} cm.$^{-1}$.

A Friedel–Crafts reaction between 10 ml. of benzene and 6 g. of benzoyl chloride containing 10 mole % of gallium trichloride yielded 27% of benzophenone after refluxing under anhydrous conditions for 4 hr. (benzophenone, m. p. 45°, b. p. 305°; 2 : 4-dinitrophenylhydrazone, m. p. 236°, mixed m. p. 237°; semicarbazone, m. p. and mixed m. p. 165°). The yield could undoubtedly be improved in the presence of a higher concentration of gallium trichloride.[31, 32]

DISCUSSION

The principal results obtained on the addition compounds of acetyl and benzoyl chlorides with the trichlorides of Group III are summarized in Table 9. The trends are towards increased stability, increased ionic nature, and increased catalytic activity of the addition compound with increasing atomic number of the electron-deficient atom. However, these trends are unlikely to continue to indium and thallium; the trihalides of these elements form few addition compounds (Gmelin), and there are indications that indium trichloride has no catalytic activity, at least in the alkylation of benzene by ethylene, under conditions where aluminium and gallium trichlorides are effective.[34] It will also be noted from Table 9 that aluminium trichloride stands much closer to gallium trichloride in its acceptor properties than it does to boron trichloride. This is due, in part, to the small size of the boron atom and the consequent anomalous properties which arise in common

[34] Ulich, Keutmann, and Geierhaas, *Z. Elektrochem.*, 1943, **49**, 292.

with all elements in the first Short Period. The effect is enhanced by the close similarity in size of aluminium and gallium due to a "*d*-block contraction" analogous to the lanthanide (or *f*-block) contraction. As a result the radii for tetrahedral covalent bonding are boron 0·89, aluminium 1·26, and gallium 1·26 Å. The similarity between the trichlorides of aluminium and gallium is also illustrated by the fact that both are dimeric, whereas boron trichloride is monomeric.

TABLE 9. *Properties of addition compounds in the binary systems of acyl chlorides with Group* III *trichlorides.*

System	M. p. of 1 : 1 compound	Vap. press. (mm. at *t*°)	Elec. cond. (ohm^{-1} $cm.^{-1}$ at *t*°)	Dipole moment (D) (solvent)	Catalytic activity
BCl_3–AcCl	−54° (dissoc.) [a]	385 (0°)	—	—	Absent
BCl_3–BzCl	No compound	320 (0°)	$<10^{-6}$ (25°)	—	Absent
$AlCl_3$–AcCl	Decomp.[16]	Low	—	—	Strong
$AlCl_3$–BzCl	95° [16, b]	Low	—	9·04 (C_6H_6) [18, d]	Strong
$GaCl_3$–AcCl	86° (decomp.)	6 (20°)	—	—	V. strong
$GaCl_3$–BzCl	46·5° [c]	0 (20°)	$1·08 \times 10^{-2}$ (45°)	6·85 (CCl_4)[3]	V. strong

[a] Ref. 20 gives −60° to −70°. [b] Ref. 17 gives 93°. [c] Ref. 3 gives 46°. [d] This value is affected by the Friedel–Crafts benzoylation of the solvent by the solute. The dipole moment [18] in carbon disulphide is 7·93 D.

The electron-donor properties of acetyl chloride enable it to co-ordinate to a variety of metal halides (magnesium bromide,[35] boron trichloride, boron trifluoride,[20, 36] aluminium trichloride,[16] gallium trichloride, titanium tetrachloride,[37, 38] tin tetrachloride,[20] and antimony pentachloride[20]), and the properties of some of these complexes may be compared with advantage. Thus, the phase diagram of the system which acetyl chloride forms with boron trichloride (Fig. 2) is strikingly similar to that of its system with titanium tetrachloride, which shows the same type of broad maximum at the equimolar ratio.[38] Again, the vapour pressure of the compound boron trichloride–acetyl chloride may be compared with that of the corresponding compound with boron trifluoride :[36]

$$BF_3,AcCl, \log p \text{ (mm).} = 15·762 - 2877/T \text{ between } -80° \text{ and } -60°$$
$$BCl_3,AcCl, \log p \text{ (mm.)} = 7·294 - 1294/T \text{ between } -70° \text{ and } +13°$$

The pressure above the boron trifluoride compound is always greater, and its heat of vaporization is about 2·2 times as large as that of its boron trichloride analogue. By contrast, boron trifluoride–acetyl fluoride has zero vapour pressure even at −50°; it dissociates quantitatively at room temperature without melting.[39] The simple and reversible dissociation into donor and acceptor components which is shown by these systems is not paralleled by the behaviour of the compounds which acetyl chloride forms with aluminium and gallium trichloride. Here, melting is accompanied by decomposition due to self-acetylation. For the complex with aluminium trichloride this may be represented by the equation [16] $3Me{\cdot}CO{\cdot}Cl + AlCl_3 \rightleftharpoons Me{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}COCl,AlCl_3 + 2HCl$. A similar reaction is considered to take place, to a much smaller extent, in the system with gallium trichloride investigated in the present work.

Benzoyl chloride forms addition compounds with all the electron acceptors mentioned in the preceding paragraph except the boron trihalides.[35, 17, 40, 38, 20] In addition, compounds have been reported with aluminium tribromide [17] and ferric chloride,[41] but a detailed comparison of properties does not appear profitable at present. It will, however, be apparent from Table 9 that the complexes of benzoyl chloride with aluminium and gallium trichloride are more stable than are the corresponding complexes of acetyl chloride with these acceptors. The reverse is true for the systems with boron trichloride as the electron acceptor molecule.

[35] Menschutkin, *Chem. Zentr.*, 1906, *II*, 1720.
[36] Brown, Schlesinger, and Burg, *J. Amer. Chem. Soc.*, 1939, **61**, 673.
[37] Bertrand, *Bull. Soc. chim. France*, 1880, **33**, 403.
[38] Cullinane, Chard, and Leyshon, *J.*, 1952, 4106.
[39] Seel, *Z. anorg. Chem.*, 1943, **250**, 331.
[40] Bertrand, *Bull. Soc. chim. France*, 1880, **34**, 631.
[41] Nencki, *Ber.*, 1899, **32**, 2414; Boeseken, *Rec. Trav. chim.*, 1903, **22**, 315.

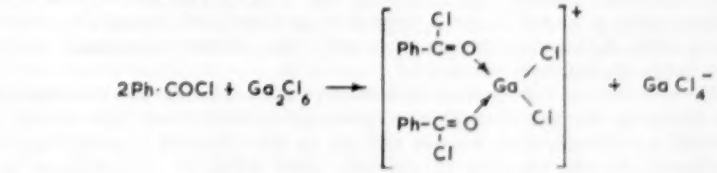
The curious phenomenon of a system which simultaneously exhibits a melting-point maximum and a positive deviation from Raoult's law has already been alluded to in presenting the results on the system boron trichloride–acetyl chloride. It appears that the 1 : 1 complex is a lattice compound which is stabilized in the solid state by favourable packing conditions but dissociates completely on melting. This demonstration of solid-compound formation between two components which show no association whatever in the liquid phase may resolve a controversy which has arisen from the apparent discrepancy that, whereas vapour pressure–composition curves for solutions of aluminium halides in alkyl halides gave no indication of compound formation at room temperature,[42] yet solid compounds each with a definite dissociation pressure were obtained [5] on similar systems at −80°. The former experiments were presumably carried out above the melting point of the labile compounds so that only positive deviations in the vapour-pressure curves were obtained.

It only remains to discuss the structure of the complexes which gallium trichloride forms with acetyl and benzoyl chloride in the solid and the liquid phases. Any elucidation of chemical constitution by means of physical properties depends for its success on the care with which the components are purified and handled. In the present work, vacuum-line techniques have been used to ensure purity of reactants and the absence of subsequent contamination by moisture. Despite these precautions, the inherent instability of molten gallium trichloride–acetyl chloride precludes the accurate measurement of significant physical properties, but the corresponding compound with benzoyl chloride is free from this drawback and reproducible results can be obtained. The high electrical conductivity of molten gallium trichloride-benzoyl chloride indicates extensive ionic dissociation and several hypothetical structures may be considered for the ions formed. The simplest of these would arise from the donation of a pair of electrons from a chloride ion to the gallium trichloride to give benzoyl tetrachlorogallate :

$$Ph{\cdot}CO{\cdot}Cl{\rightarrow}GaCl_3 \rightleftharpoons Ph{\cdot}CO^+ + GaCl_4^-$$

This structure would explain the electrical conduction and catalytic action in a straightforward way which is now generally accepted.[43] It is also consistent with the fact that the corresponding compounds with boron trichloride do not occur in the liquid phase, since these would involve the unstable tetrachloroborate anion, the existence of which has yet to be established unambiguously in any compound. This instability of the tetrachloroborate ion is presumably related to the small size of the boron atom as mentioned earlier in the Discussion, but it is not a direct steric effect, for a simple model will demonstrate that it is possible to pack even four iodine atoms tetrahedrally about boron (cf. also the existence of carbon tetraiodide).

An alternative structure for the addition compounds of Group III elements has been suggested by Lebedev [44] on the basis of properties which are shown by the complexes of aluminium bromide with acyl bromides. However, the arguments used do not appear to be conclusive, nor the experiments crucial. Applied to the present system the structure would be written as follows :



This structure has no advantages over the previous one and makes the interpretation of catalysis more complicated. Two further structures involving either chlorine or oxygen as the ligand are conceivable, $[Ph{\cdot}CO{\cdot}Cl{\rightarrow}GaCl_2]^+Cl^-$ and $[Ph{\cdot}CCl{=}O{\rightarrow}GaCl_2]^+Cl^-$.

[42] Van Dyke, *J. Amer. Chem. Soc.*, 1950, **72**, 3619.
[43] Burton and Praill, *Quart. Rev.*, 1952, **6**, 302.
[44] Lebedev, *J. Gen. Chem. (U.S.S.R.)* (U.S. Transl.), 1951, **21**, 1975.

However, these suffer the defect that the gallium atom is still electron-deficient and therefore unlikely to exist in the presence of a dissociating chloride ion unless a more powerful electron-donor solvent were present to stabilize the gallium by co-ordination.[45] In the absence of a solvent, such systems would tend to form quadricovalent molecules, which does not accord with the high conductivity of the molten complex. The principal structural feature which distinguishes the first mode of ionization as benzoyl tetrachlorogallate from the other hypothetical modes is that only for this first scheme does all the gallium appear in the anion. Tracer experiments with ^{72}Ga have been designed to follow the migration of the ions during electrolysis of the molten complex and the results will be published later.

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THE UNIVERSITY, NOTTINGHAM. [*Received, November 28th*, 1955.]

[45] Van Dyke, *J. Amer. Chem. Soc.*, 1950, **72**, 2823.

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307. *Correlation between Reactivity of the 1-Carbon Atom in Alcohols, and Certain Properties of Alkoxysilanes.*

By W. GERRARD and K. D. KILBURN.

The rate at which the entity ROH_2Cl forms alkyl chloride or hinders replacement of chlorine attached to silicon is important in chlorosilane systems. Alcohols with a phenyl group attached to the 1-carbon atom give alkyl chloride quickly, thus hindering formation of alkoxysilanes, and hydrogen chloride reacts with the silanes to give alkyl chloride directly or *via* the alcohol. Alcohols with a more remote phenyl group behave as does butan-1-ol, taken as an arbitrary standard of ordinary reactivity. Interaction between an alkoxytrimethylsilane and silicon tetrachloride gave chlorosilanes from 1-phenylethanol and diphenylmethanol, the first reported examples of chloro-esters of reactive alcohols in inorganic non-metal halide systems.

THE reactivity of the 1-carbon atom in an alcohol is governed by the kind as well as the number of substituents attached to it.[1, 2] In silane chemistry alcohols containing a phenyl group remote from the 1-carbon atom (excluding examples in which a double bond is interposed) behave as *n*-butanol, considered as an arbitrary standard of *ordinary* reactivity, and afford the tetra-alkoxysilane with silicon tetrachloride alone,[3] whereas those with a phenyl group attached to the 1-carbon atom (except benzyl alcohol which is somewhat peculiar) give alkyl chloride and silica, accompanied in some cases by other products. Thus 1-phenylethanol gives alkyl chloride and hydrated silica,[4] as *tert.*-butyl alcohol does; diphenylmethanol gives chlorodiphenylmethane and bisdiphenylmethyl ether; [3] yet benzyl alcohol gives the alkoxysilane. Probably owing to an electromeric effect the silane could not be obtained from cinnamyl alcohol in absence of base. In the presence of pyridine the tetra-alkoxysilanes were prepared in good yield from primary and secondary alcohols, whereas reaction with 2-phenylbutan-2-ol gives only the dialkoxy-compound, as has previously been shown for *tert.*-butyl alcohol.[4, 5]

With trimethylchlorosilane the reactive alcohols gave alkyl chloride, and the others did not give good yields of alkoxytrimethylsilane, presumably because of intervention by hydrogen chloride, and attempts to remove the gas at low pressure removed also the volatile chlorosilane. In the presence of pyridine, good yields of alkoxysilanes were obtained (see Table).

[1] Gerrard and Shepherd, *J.*, 1953, **2069**; Gerrard, Green, and Phillips, *J.*, 1954, 1148; Gerrard and Howe, *J.*, 1955, 505.
[2] Gerrard, Madden, and Tolcher, *J. Appl. Chem.*, 1955, **5**, 28.
[3] Gerrard and Kilburn, *Research*, 1954, **7**, 57 s.
[4] Gerrard and Woodhead, *J.*, 1951, 519.
[5] Miner, Brian, Holysz, and Pedlow, *Ind. Eng. Chem.*, 1947, **39**, 1368.

Preparation of alkoxytrimethylsilanes.

Alcohol	Yield (%)	B. p./mm.	d_4^{20}	n_D^{20}	Found C (%)	Found H (%)	$(CH_3)_3Si{\cdot}OR$ requires C (%)	$(CH_3)_3Si{\cdot}OR$ requires H (%)
Bu^{t}OH	78	101°/754	—	1·3913	57·6	12·1	57·6	12·3
Benzyl alcohol	84	92°/19	0·9205	1·4773	67·4	8·9	66·7	8·9
2-Phenylethanol	85	102°/18	0·9086	1·4739	68·2	9·3	68·1	9·3
3-Phenylpropanol	88	118°/19	0·9073	1·4744	69·7	9·8	69·3	9·6
1-Phenylethanol	85	91°/14	0·9059	1·4702	68·1	9·1	68·1	9·3
1-Phenylpropan-2-ol	79	102°/18	0·8974	1·4690	69·5	9·6	69·3	9·6
Cinnamyl alcohol	79	128°/15	0·9375	1·5105	69·8	8·8	69·8	8·7
2-Phenylbutan-2-ol	72	108°/16	0·9153	1·4805	71·1	9·8	70·4	9·9
Diphenylmethanol	89	111°/0·6	0·9903	1·5290	75·5	7·5	74·9	7·8
1 : 2-Diphenylethanol	85	90°/0·005	0·9733	1·5198	76·1	8·2	75·6	8·15
1 : 3-Diphenylpropan-2-ol	70	99°/0·02 (m. p. 35°)	0·9864	1·5281	76·4	8·15	76·0	8·45

Analogously with the interaction of hydrogen chloride and the tetra-alkoxysilanes,[3] the alkoxytrimethylsilanes, afforded trimethylchlorosilane and either the alcohol from esters with a remotely attached phenyl group (except cinnamyl derivative), or the alkyl chloride from esters with a 1-phenyl group (but also the cinnamyl compound), and in the latter cases it is conceivable that alcohol is first formed and then quickly converted into alkyl chloride.

The interaction of a tetra-alkoxysilane and silicon tetrachloride has long been formulated as a means of preparing alkoxychlorosilanes, but the reaction is slow even at 150° for the *n*-butyl ester,[6] and we now show that with the (phenylalkoxy)silanes reaction occurs slowly at 60° (7 days), those with a 1-phenyl group giving alkyl chloride, those with a more remote group giving chlorosilanes. Of more interest is the quicker interaction of silicon tetrachloride (1 mol.) and the alkoxytrimethylsilanes (4 mols.) :

$$Me_3Si{\cdot}OR + SiCl_4 \longrightarrow Me_3SiCl + RO{\cdot}SiCl_3$$
$$Me_3Si{\cdot}OR + RO{\cdot}SiCl_3 \longrightarrow Me_3SiCl + (RO)_2SiCl_2 \dashrightarrow (RO)_4Si$$

Silanes with a remote phenyl group give the tetra-esters. The tetra-ester was obtained from the benzyl ester, but from the 1-phenylethyl ester chlorotri-(1-phenylethoxy)silane was obtained. This is the first recorded example of such a chloro-ester in the 1-phenylethanol–inorganic non-metal halide systems. We attribute success in this instance to the complete absence of hydrogen chloride. Similar remarks apply to chlorotri(diphenylmethoxy)silane which was likewise obtained. Even the 2-phenylbutan-2-ol ester afforded trimethylchlorosilane and a product which did not decompose until heated to 130°, whereupon it gave 2-phenylbut-2-ene. The cinnamyl ester gave the tetra-ester, and the 1 : 3-diphenylpropan-2-ol ester gave the dichlorosilane.

The alkoxytriphenylsilane system was examined, but gave no additional information of relevance.

Experimental

Tetra-alkoxysilanes.—The silanes used were those already described ; [3] *tetracinnamyloxysilane* (crude, 95% ; pure, 81%), m. p. 84° (from *n*-hexane) (Found : C, 76·5 ; H, 6·5 ; Si, 5·0. $C_{36}H_{36}O_4Si$ requires C, 77·2 ; H, 6·4 ; Si, 5·0%), was obtained from the alcohol (4 mols.), pyridine (4 mols.) and silicon tetrachloride (1 mol.). 2-Phenylbutan-2-ol gave slowly a precipitate of pyridine hydrochloride in only 50% yield ; violent decomposition occurred at 125°/0·2 mm. Tetrabenzyloxysilane had m. p. 31·5° (from *n*-hexane at −60°).

Passage of hydrogen chloride into a suspension of tetracinnamyloxysilane in *n*-hexane at 20° gave cinnamyl chloride (53%), b. p. 42°/0·02 mm. (Found : Cl, 22·8. Calc. for C_9H_9Cl : Cl, 23·2%). The silane could not be obtained by the interaction of cinnamyl alcohol and silicon tetrachloride in ether at 20°.

Silicon tetrachloride (1 mol. ; in ether, 10 mols.) was added dropwise to 2-phenylbutan-2-ol (23·6 g., 1 mol. ; in ether, 50 mols.) at 20°. Volatile matter was immediately withdrawn at 20°/15 mm., hydrogen chloride (83%) being evolved, and the residue was extracted with *n*-hexane. The final residue, on ignition, gave silica (94%). The solution afforded 2-phenylbut-2-ene (96%), b. p. 77°/15 mm., n_D^{20} 1·4345 (Found : C, 90·6 ; H, 9·3. Calc. for $C_{10}H_{12}$:

[6] Gerrard and Jones, *J.*, 1952, 1690.

C, 90·9; H, 9·1%), oxidised by potassium permanganate to acetophenone (3 : 5-dinitrophenylhydrazone, m. p. 237—238°).

Interaction of Silicon Tetrachloride and Tetra-alkoxysilanes.—The tetrachloride (1 mol.) and tetrabenzyloxysilane (1 mol.) were mixed; the container was sealed and kept at 60° for 7 days. Soluble matter was extracted by *n*-hexane in a Soxhlet apparatus, and on ignition the residue afforded silica (82%). Benzyl chloride (88%), b. p. 64°/12 mm. (Found: Cl, 27·8. Calc. for C_7H_7Cl: Cl, 28·0%), was obtained from the solution.

Tetra-(1-phenylethoxy)silane (7·86 g. 1 mol.) gave silica (92%), α-chloro-1-phenylethane (1·32 g.), b. p. 64°/10 mm. (Found: Cl, 25·0. Calc. for C_8H_9Cl: Cl, 25·3%), and polystyrene (3·73 g.). (Extraction was by chloroform.)

Tetracinnamyloxysilane (4·52 g., 1 mol.) gave silica (98%), cinnamyl chloride (0·95 g.), b. p. 60°/0·07 mm., n_D^{20} 1·5642 (Found: Cl, 23·4. Calc. for C_9H_9Cl: Cl, 23·3%), and other products. (Extraction was by chloroform.)

Tetra(diphenylmethoxy)silane (4·02 g., 1 mol.) gave silica (68%), diphenylmethyl chloride (2·58 g.), b. p. 106°/0·4 mm., n_D^{20} 1·5960 (Found: Cl, 17·3. Calc. for $C_{13}H_{11}Cl$: Cl, 17·5%), and a residue (1·0 g.). (Extraction was by ether.)

Tetra-(1 : 2-diphenylethoxy)silane (3·40 g.) gave hydrogen chloride at considerable pressure in the tube. Silica (99%), 1 : 2-diphenylethyl chloride (0·21 g.), which could not be purified, and *sym*-hexaphenyl*cyclo*hexane (1·12 g.), b. p. 229°/0·03 mm. (Found: C, 92·6; H, 7·1. Calc. for $C_{42}H_{36}$: C, 93·4; H, 6·6%) (Found: *M*, 527. Calc.: *M*, 540), were obtained. (Extraction was by *n*-pentane, then chloroform.)

Tetra-(2-phenylethoxy)silane (6·65 g.) gave a mixture from which unchanged silicon tetrachloride (1·21 g.) was removed at 20°/0·07 mm., and then *trichloro-2-phenylethoxysilane* (1·39 g.), b. p. 74—80°/0·07 mm., n_D^{20} 1·4950 (Found: Cl, 40·6; Si, 10·7. $C_8H_9OCl_3Si$ requires Cl, 41·7; Si, 10·9%), mixtures of the lower chlorosilanes containing diminishing amounts of chlorine and silicon, unchanged alkoxysilane (3·0 g.), and a residue (1·26 g.) were obtained.

Tetra-3-phenylpropoxysilane (7·10 g.) gave *trichloro-3-phenylpropoxysilane* (0·34 g.), b. p. 40°/0·02 mm. (Found: Cl, 38·9. $C_9H_{11}OCl_3Si$ requires Cl, 39·5%), *dichlorodi-(3-phenylpropoxy)silane* (0·28 g.), b. p. 140°/4 × 10^{-3} mm., n_D^{20} 1·5224 (Found: Cl, 19·3; Si, 7·5. $C_{18}H_{22}O_2Cl_2Si$ requires Cl, 19·3; Si, 7·6%), and mixtures (total, 4·5 g.) of the latter with the monochlorosilane.

Tetra-(1-methyl-2-phenylethoxy)silane (7·16 g.) gave *trichloro-1-methyl-2-phenylethoxysilane* (0·54 g.), b. p. 56°/0·03 mm. (Found: Cl, 38·6. $C_9H_{11}OCl_3Si$ requires Cl, 39·5%), *dichlorodi-(1-methyl-2-phenylethoxy)silane* (5·9 g.), b. p. 111°/0·01 mm., n_D^{20} 1·5144, d_4^{20} 1·1340 (Found: C, 59·3; H, 6·0; Cl, 19·4; Si, 7·6. $C_{18}H_{20}O_2Cl_2Si$ requires C, 58·7; H, 6·0; Cl, 19·3; Si, 7·6), a mixture (1·52 g.) of this silane with monochlorosilane, and a residue (1·24 g.) (Found: Si, 9·7%).

Tetra-1-benzyl-2-phenylethoxysilane (4·55 g.) gave mixtures of chlorosilanes which were difficult to fractionate. The impure trichlorosilane (1·16 g.), b. p. 114—116°/0·01 mm., *di-(1-benzyl-2-phenylethoxy)dichlorosilane* (1·32 g.), b. p. 210°/0·01 mm., n_D^{20} 1·5645, d_4^{20} 1·445 (Found: Cl, 13·7; Si, 5·2. $C_{30}H_{30}O_2Cl_2Si$ requires Cl, 13·6; Si, 5·4%), tri-(1-benzyl-2-phenylethoxy)-chlorosilane (0·42 g.), b. p. 240—250°/0·01 mm. (Found: Si, 4·0. Calc. for $C_{45}H_{45}O_3ClSi$: Si, 4·0%), and a residue (1·58 g.) were obtained.

Preparation of Alkoxytrimethylsilanes.—Trimethylchlorosilane (1 mol.) in ether (4 mols.) was added dropwise to the alcohol (1 mol.) and pyridine (1 mol.) in ether (30 mols.) at 15°. Only 80—85% (or less in some cases) of the calculated amount of pyridine hydrochloride was immediately precipitated, and even after the mixture had been set aside for 12 hr., the yield was nearly always less than 95%. This corresponded with the presence of about 5% of alcohol, and owing to the formation of an azeotrope a considerable amount of the silane had to be rejected during distillation. Consequently the yields given in the Table are less than the amounts of silanes actually formed. Alcohol in the crude product was also removed by heating the liquid with pyridine and chlorosilane for 2 hr. at 60°. The product was decanted from the base hydrochloride, and distilled.

Interaction of Hydrogen Chloride and Alkoxytrimethylsilane.—Dry hydrogen chloride was passed into the ester for 90 min. at −10°; trimethylchlorosilane (77—90% yield) was trapped at −80°. There were mainly two types of result: formation of alcohol, Bu^n, Ph·CH_2·CH_3, Ph·CH_2·CH_2·CH_3, $(Ph·CH_2)_2CH$, Ph·CH_2·CHPh; or formation of alkyl chloride, Ph·CH_2, Ph·CHMe, Ph·CH_2·CHMe, Ph·CH:CH·CH_3, Ph·CEtMe, Ph_2CH.

Interaction of Silicon Tetrachloride and Alkoxytrimethylsilane.—The tetrachloride (1 mol.) and alkoxysilane (4 mols.) were mixed at room temperature. After the stated time interval, trimethylchlorosilane was withdrawn at 0·3 mm. and trapped at −80° (Found: Cl, 32·4 ± 0·4%), and the residue was distilled.

The benzyl ester (9·00 g.) (24 hr.) gave tetrabenzyloxysilane (4·38 g.), b. p. 210—212°/0·1 mm., n_D^{20} 1·5599 (Found : Si, 6·2. Calc. for $C_{28}H_{25}O_4Si$: Si, 6·1%); the 2-phenylethyl ester (9·70 g.) (2·5 hr.) gave tetra-(2-phenylethoxy)silane (5·46 g.), b. p. 226°/10^{-3} mm., n_D^{20} 1·5480 (Found : Si, 5·7. Calc. for $C_{32}H_{36}O_4Si$: Si, 5·5%); the 3-phenylpropyl ester (10·4 g.) (16 hr.) gave tetra-3-phenylpropoxysilane (5·88 g.), b. p. 186—195°/10^{-5} mm., n_D^{19} 1·5402 (Found : C, 76·8; H, 7·8; Si, 5·1. Calc. for $C_{36}H_{44}O_4Si$: C, 76·2; H, 7·75; Si, 4·9%); the 1-phenylethyl ester (3·59 g.) (14 hr.) gave *chlorotri-(1-phenylethoxy)silane* (1·80 g.), b. p. 185°/0·07 mm., n_D^{20} 1·5347 (Found : Cl, 8·0; Si, 6·5. $C_{24}H_{27}O_3ClSi$ requires Cl, 8·3; Si, 6·6%); and the 1-methyl-2-phenylethyl ester (10·4 g.) gave a very slowly separable mixture (1·23 g.), b. p. 180—210°/5 × 10^{-3} mm., of chlorosilane and tetra-ester (Found : Cl, 6·1%), and tetra-(1-methyl-2-phenylethoxy)silane (5·02 g.), b. p. 210—212°/5 × 10^{-3} mm., n_D^{20} 1·5312 (Found : Si, 5·0. Calc. for $C_{36}H_{44}O_4Si$: Si, 4·9%). The cinnamyl ester (9·5 g.) (16 hr.) evolved heat on mixing and eventually gave a white solid which after being crushed gave trimethylchlorosilane (2·31 g.) and tetracinnamyloxysilane (5·47 g.), m. p. 84—85° (from *n*-hexane) (Found : C, 76·5; H, 6·4; Si, 5·1. Calc. for $C_{36}H_{36}O_4Si$: C, 77·2; H, 6·4; Si, 5·0%). The diphenylmethyl ester (13·6 g.) (14 hr.) gave *chlorotri(diphenylmethoxy)silane* (5·71 g.), m. p. 99—100° (from *n*-heptane) (Found : C, 76·4; H, 5·8; Cl, 5·7; Si, 4·5. $C_{39}H_{33}O_3ClSi$ requires C, 76·4; H, 5·4; Cl, 5·8; Si, 4·6%).

The 1-methyl-2-phenylethyl ester (5·23 g.) (3 hr.) gave unchanged ester (1·57 g.), and dichlorodi-(1-methyl-2-phenylethoxy)silane (2·34 g.) b. p. 240—250°/0·03 mm., n_D^{20} 1·5755 (Found : Cl, 12·5; Si, 5·2. Calc. for $C_{30}H_{30}O_2Cl_2Si$: Cl, 13·6; Si, 5·4%). The 1 : 2-diphenylethyl ester (1·92 g.) (16 hr.) gave decomposition products, comprising alkyl chloride and stilbene, m. p. 123—125° (from *n*-hexane). The 1-methyl-1-phenylpropyl ester (11·1 g.) (5 days) gave trimethylchlorosilane (1·45 g.), and at 130° violent effervescence occurred, silica (ignited, 0·70 g., 95%) was precipitated, and trimethylchlorosilane (3·02 g.), 2-phenylbut-2-ene (4·0 g.), b. p. 78°/14 mm., n_D^{20} 1·5290 [oxidised by chromium trioxide in acetic acid to acetophenone (2 : 4-dinitrophenylhydrazone, m. p. 238°)], and a mixture (2·92 g.) of 2-phenylbut-2-ene and 2-chloro-2-phenylbutane, b. p. 78—82°/14 mm. (Found : Cl, 6·8%), were obtained.

tert.-*Butoxysilanes*.—Hydrogen chloride was passed into *tert.*-butoxytrichlorosilane b. p. 132—134°, n_D^{20} 1·4145 (Found : Cl, 51·1. Calc. for $C_4H_9OCl_3Si$: Cl, 51·4%) (7·76 g.), for 6 hr. at 21°, and *tert.*-butyl chloride (35%), b. p. 50—51° (Found : Cl, 37·8. Calc. for C_4H_9Cl : Cl, 38·4%), was trapped at −80°, leaving a viscous gel (6·0 g.).

Hydrogen chloride was passed into di-*tert.*-butoxydichlorosilane, b. p. 62°/10 mm. (Found : Cl, 28·7. Calc. for $C_8H_{18}O_2Cl_2Si$: Cl, 28·9%) (13·7 g.), for 2 hr. at 6°, and *tert.*-butyl chloride (81%), b. p. 50—51° (Found : Cl, 37·7%), was condensed at −80°.

The dichlorosilane (7·3 g., 1 mol.) and *tert.*-butyl alcohol (4·4 g., 2 mols.), heated under reflux at 80° for 1 hr., gave *tert.*-butyl chloride (4·25 g.), b. p. 50—51° (Found : Cl, 37·8%), and silica gel (2·2 g.) (ignited to silica, 1·40 g., 78%).

Alkoxytriphenylsilanes.—These were prepared from the alcohol (1 mol.), pyridine (1 mol.), and triphenylchlorosilane (1 mol.) in ether (30 mols.) at 0°, base hydrochloride being precipitated much more slowly than with trimethylchlorosilane.

Hydrogen chloride was passed into *triphenyl-2-phenylethoxysilane*, b. p. 185°/0·01 mm., m. p. 56—57° (after recrystallisation from *n*-heptane at −60°) (Found : C, 82·2; H, 6·2; Si, 7·4. $C_{26}H_{24}OSi$ requires C, 82·2; H, 6·3; Si, 7·4%) (3·72 g.) in *n*-heptane (15 c.c.) at 16° for 1 hr. Chlorotriphenylsilane (38%) was filtered off and 2-phenylethanol (36%), b. p. 45°/0·05 mm., and unchanged silane (60%) were obtained from the filtrate. From the silane (5·07 g., 4 mols.) and tetrachloride (1 mol.) (sealed tube at 60° for 7 days), the chlorotriphenylsilane (80%), m. p. 104°, and tetra-2-phenylethoxysilane (1·93 g.), b. p. 250°/0·03 mm. (Found : Si, 5·6. Calc. for $C_{32}H_{36}O_4Si$: Si, 5·5%), were obtained. Similarly benzyloxytriphenylsilane (3·3 g.) gave chlorotriphenylsilane (83%), m. p. 104—105° (Found : Cl, 11·9; Si, 9·55. Calc. for $C_{18}H_{15}ClSi$: Cl, 12·0; Si, 9·5%), unchanged silane (0·6 g.) (Found : Si, 7·7%), and tetrabenzyloxysilane (0·6 g.), b. p. 210°/0·01 mm. (Found : Si, 6·3. Calc. for $C_{28}H_{28}O_4Si$: Si, 6·1%). *Diphenylmethoxytriphenylsilane* (64%): b. p. 210—212°/0·01 mm., n_D^{20} 1·6252, d_4^{20} 1·085 (Found : C, 84·4; H, 5·8. $C_{31}H_{26}OSi$ requires C, 84·2; H, 5·9%) (2·20 g.), afforded hexaphenyldisiloxane (0·62 g.), m. p. 230° (from *n*-heptane) (Found : C, 81·5; H, 5·8. Calc. for $C_{36}H_{30}O_2Si$: C, 80·9; H, 5·6%), diphenylmethyl chloride (49%), b. p. 99—100°/0·2 mm., n_D^{20} 1·5978 (Found : Cl, 17·0. Calc. for $C_{13}H_{11}Cl$: Cl, 17·5%), and unchanged silane (0·39 g.), b. p. 200—220°/0·2 mm.

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308. *Stability, Solvolysis, and Co-ordination Reactions of Esters of Boronic Acids and their Halogen Derivatives.*

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Esters of *n*-butyl- and phenyl-boronic acid $R{\cdot}B(OR')_2$ and *n*-butyl *n*-butyl- and phenyl-halogenoboronite $R{\cdot}BHal{\cdot}OR'$, and *n*-butyl(and phenyl)-boron dihalides $R{\cdot}BHal_2$, have been studied in respect of their thermal stability, hydrolysis, alcoholysis, and co-ordination (action of pyridine) reactions. Where evidence is available, mechanisms are suggested and the general resemblance of these three classes to respectively borates, alkoxy-boron halides, and boron trihalides is pointed out.

In continuation of the study [1,2] of esters, $R{\cdot}B(OR')_2$, and halogeno-esters, $R{\cdot}BHal{\cdot}OR'$, of alkyl- or aryl-boronic acids and of alkyl- or aryl-boron dihalides, $R{\cdot}BHal_2$, we have examined the hydrolysis, alcoholysis, thermal stability, and co-ordination reactions of these compounds, wherein R = Bu^n or Ph and Hal = F or Cl.

That esters of boronic acids are hydrolysed to the parent acids [see (1)] is known. Esters of alkylboronic acids are hydrolysed more slowly than those of arylboronic acids and also than esters of boric acid, and this may be utilised in the separation of alkyl-

$$R{\cdot}B(OR')_2 + 2H_2O \longrightarrow 2R{\cdot}B(OH)_2 + 2R'OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

boronates from trialkyl borates.[1] Such hydrolysis might involve either alkyl–oxygen or boron–oxygen fission. The latter is probably the usual mechanism because di-(+)-2-methylheptyl phenylboronate afforded the (+)-alcohol, without loss of activity, and di*neo*-pentyl phenylboronate gave *neo*pentyl, and not a rearranged, alcohol. The configuration and maximum activity of the (+)-2-methylheptyl phenylboronate were calculated on the assumption that its preparation from phenylboron dichloride and (+)-octan-2-ol [see (10)] occurs with complete retention of configuration, as this appears not to involve substitution at the asymmetric carbon atom.

Alcoholysis of boronates [see (2)] led to exchange of alkoxy-groups when the alcohol used had a higher boiling point than the alcohol of the original ester. This was demonstrated by the high yields of *n*-, *iso*-, and *sec*.-butyl phenylboronate obtained from diethyl

$$R{\cdot}B(OR')_2 + 2R''OH \rightleftharpoons R{\cdot}B(OR'')_2 + 2R'OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

phenylboronate. This reaction also probably involved boron–oxygen fission, because (+)-2-methylheptyl phenylboronate was obtained when (+)-octan-2-ol interacted with diethyl phenylboronate.

There was no evidence for compound formation between pyridine and *n*-butyl phenyl- or *n*-butyl-boronate, but a stable 1 : 1 complex was obtained with di-(2 : 2 : 2-trichloroethyl) phenylboronate. That the electron-attracting chlorine atoms have increased the availability of boron for co-ordination with nitrogen would be a plausible enough explanation were it not that tri(-2 : 2 : 2-trichloroethyl)borate, like other borates (except trimethyl or triaryl borates [3]), gave no such complex; the explanation would be valid if steric hindrance to approach to the boron atom in the heavily chlorinated borate were responsible for this inactivity.

Hydrolysis, as well as *n*-butyl-alcoholysis, of *n*-butyl *n*-butylchloroboronite afforded

$$2Bu^n{\cdot}BCl{\cdot}OBu^n + 2H_2O \longrightarrow 2HCl + Bu^n{\cdot}B(OBu^n)_2 + Bu^n{\cdot}B(OH)_2 \quad . \quad . \quad . \quad (3)$$

$$Bu^n{\cdot}BCl{\cdot}OBu^n + Bu^nOH \longrightarrow HCl + Bu^n{\cdot}B(OBu^n)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

di-*n*-butyl *n*-butylboronate [see (3) and (4)]. Whereas addition of *n*-butyl phenylchloroboronite to an excess of pyridine afforded an unstable 1 : 2 complex, which may have an

[1] Brindley, Gerrard, and Lappert, *J.*, 1955, 2956.
[2] *Idem*, *ibid.*, 1956, 824.
[3] Colclough, Gerrard, and Lappert, *J.*, 1955, 907.

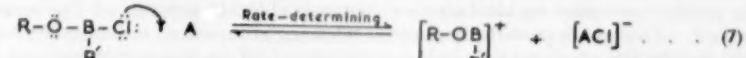
ionic structure, $(Ph{\cdot}B{\cdot}OBu^n,2py)^+Cl^-$, the addition of pyridine (1 mol.) to *n*-butyl *n*-butylchloroboronite (2 mols.) led to disproportionation [see (5)].

$$2Bu^n{\cdot}BCl{\cdot}OBu^n + py \longrightarrow Bu^n{\cdot}BCl_2{,}py + Bu^n{\cdot}B(OBu^n)_2 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Both *n*-butyl phenylchloroboronite and *n*-butyl *n*-butylchloroboronite were stable for 3 hr. at 100° but decomposed slowly at 200°, the former compound being the more stable. In both cases traces of anhydrous ferric chloride catalysed the decomposition, and a rapid reaction at 20° [see (6)] was then observed. Similar decomposition of (+)-2-methylheptyl

$$R{\cdot}BCl{\cdot}OBu^n \longrightarrow R{\cdot}BO + Bu^nCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

phenylchloroboronite afforded (−)-2-chloro-octane, with little loss of activity. The decomposition of these compounds probably involves a rate-determining B–Cl heterolysis which is catalysed by Lewis acids [designated "A" in (7)], subsequent alkyl halide formation then taking place by an in-line S_N2 mechanism (8).



$$\text{Rate-determining} \quad . \quad . \quad . \quad (7)$$

$$. \quad . \quad . \quad (8)$$

n-Butyl phenyl- and *n*-butyl-fluoroboronite underwent hydrolysis in an excess of water to the boronic acid and hydrogen fluoride, as indicated by acidimetric estimation for boron and fluorine. Addition of pyridine to the esters effected disproportionation [analogous to (5)]. When *n*-butyl *n*-butylfluoroboronite was heated at 80° for 5 hours complete disproportionation [see (9)] occurred (see also ref. 2).

$$2Bu^n{\cdot}BF{\cdot}OBu^n \longrightarrow Bu^n{\cdot}BF_2 + Bu^n{\cdot}B(OBu^n)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

It has previously been demonstrated in a few isolated examples that alkyl- or aryl-boron dichlorides on alcoholysis give alkyl- or aryl-boronic esters.[4] It is now shown that this is a step-wise reaction [see (10) and (11)], involving the alkyl alkyl(or aryl)chloroboronite as an intermediate, and the product isolated is determined by the relative proportion of reagents used. Further, the influence of branching in the alcohol must be considered. Thus, whereas each of *n*-, *iso*-, and *sec*.-butyl alcohol and octan-2-ol (2 mols.) with phenylboron dichloride (1 mol.) gave high yields of the respective ester, *tert*.-butyl alcohol gave a

$$Ph{\cdot}BCl_2 + ROH \longrightarrow HCl + Ph{\cdot}BCl{\cdot}OR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$Ph{\cdot}BCl{\cdot}OR + ROH \longrightarrow HCl + Ph{\cdot}B(OR)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

$$Ph{\cdot}BCl_2 + 2Bu^tOH \longrightarrow 2Bu^tCl + Ph{\cdot}B(OH)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

low yield of ester and a side-reaction (12) produced *tert*.-butyl chloride. This difference may be due to attack of the hydrogen chloride formed on di-*tert*.-butyl phenylboronate,[2] to low stability of *tert*.-butyl phenylchloroboronite (5), or to the ease with which *tert*.-butyl alcohol reacts with hydrogen chloride. The side-reaction (12) was avoided when the reaction was carried out in presence of pyridine (see also ref. 1): $Ph{\cdot}BCl_2 + 2ROH + 2py \longrightarrow Ph{\cdot}B(OR)_2 + 2py,HCl$. This reaction does not involve a pyridine–phenylboron dichloride complex as an intermediate, because the above reaction is instantaneous at −70°, whereas reaction of such a 1 : 1 complex with alcohol and pyridine is slow even at

$$Ph{\cdot}BCl_2{,}py + 2Bu^nOH + py \longrightarrow Ph{\cdot}B(OBu^n)_2 + 2py,HCl \quad . \quad . \quad . \quad . \quad (13)$$

20°. Easters can be prepared from the complex, however, as shown in scheme (13) if the reagents are heated in chloroform for 6 hr.

Pyridine with phenylboron dichloride afforded a stable, solid 1 : 1 complex. Neither

[4] Michaelis and Becker, *Ber.*, 1880, **13**, 58; 1882, **15**, 180.

this complex nor its *n*-butyl analogue was soluble, or hydrolysed, in cold water. *n*-Butylboron difluoride gave with pyridine a liquid 1 : 1 complex.

Phenylboron dichloride and *n*-butylboron difluoride are colourless liquids which fume in air, being apparently hydrolysed quantitatively to hydrogen halide and the boronic acid, as was indicated by acidimetric estimations for halogen and boron.

The general similarity [2] of boronates and borates is further demonstrated by the present experiments. Similarities between the halogen derivatives of these esters are also observed. Thus hydrolysis of borates normally involves boron–oxygen fission.[5,6] Alcoholysis of borates causes alkoxy-exchange. Hydrolysis and alcoholysis of dichloroboronites, $Cl_2B{\cdot}OR$, and chloroboronates, $ClB(OR)_2$, result in evolution of hydrogen chloride and hydroxylation or alkoxylation respectively, of the boron atom.[7,8] These esters with pyridine give stable (usually 1 : 1) complexes,[3,9,10] and are thermally decomposed to alkyl chloride; this decomposition is catalysed by traces of Lewis acids such as ferric chloride.[4,7,8] *n*-Butyl difluoroboronite does not give a complex with pyridine, but disproportionation is observed, which also takes place when the compound is heated alone.[11] The nature of the product obtained on alcoholysis of boron trichloride depends on the branching in the alcohol. Those with powerfully electron-releasing groups (*e.g.*, *tert.*-butyl or 1-phenylethyl) give largely the alkyl chloride, whereas others afford hydrogen chloride and alkoxylation of the boron atom.[5,12] When pyridine is used, only alkoxylation is observed,[5,9] but the reaction does not proceed through a pyridine–boron trichloride complex [9] although the use of such a complex for the preparation of borates is general.[13] It thus appears that considerable resemblances in properties exist between (*a*) boronates and borates, (*b*) alkyl alkyl(or aryl)halogenoboronites, alkyl dihalogenoboronites, and dialkyl chloroboronates, and (*c*) alkyl(or aryl)boron dihalides and boron trihalides.

Experimental

General Procedures.—Boronic esters were prepared by the methods described previously.[1] Pyridine was estimated by steam-distillation from sodium hydroxide solution and titration of the distillate with sulphuric acid (bromophenol-blue). Other analytical procedures and the preparations of *n*-butyl *n*-butylhalogenoboronites, *n*-butyl phenylhalogenoboronites, *n*-butylboron difluoride, and phenylboron dichloride were as described elsewhere.[3] Rotatory powers are recorded for $l = 10$ cm.

Hydrolysis of Boronic Esters.—(a) *Dineopentyl phenylboronate.* *neo*Pentyl alcohol [4·1 g., 77% based on (I)], b. p. 111°, m. p. 58°, was steam-distilled from a mixture of the ester (8·0 g.) and an aqueous solution of sodium hydroxide, the steam-distillate being extracted with ether, and the extract dried ($MgSO_4$) and fractionally distilled.

(b) *Di-(+)-2-methylheptyl phenylboronate.* When the ester (1·08 g.) was shaken with water (10 c.c.) and *n*-pentane (10 c.c.) for 1 hr., only slight hydrolysis took place, but after the ester (1·31 g.; α_D^{20} +15·08°) had been heated under reflux with 20% aqueous potassium hydroxide (10 c.c.) for 1 hr., extraction with *n*-pentane afforded (+)-octan-2-ol [0·74 g., 98% based on (I)], b. p. 80°/13 mm., n_D^{20} 1·4259, α_D^{20} +7·58°.

Alcoholysis of Diethyl Phenylboronate.—The ester (1 mol., 0·02—0·05 molar scale) was heated with the appropriate alcohol (2·1 mols.). The lower fractions of ethanol and any unchanged alcohol were removed at 1 atm. and subsequent fractional distillation at reduced pressure afforded the new *boronate*. The results are shown in Table 1.

In the experiment with octan-2-ol, the alcohol had α_D^{20} +7·58° and the ester α_D^{20} +15·08°.

Interaction of Pyridine and Boronic Esters.—That pyridine and neither di-*n*-butyl *n*-butylboronate nor di-*n*-butyl phenylboronate formed a complex at 20° was demonstrated by adding

[5] Scattergood, Miller, and Gammon, *J. Amer. Chem. Soc.*, 1945, **67**, 2150.
[6] Gerrard and Lappert, *J.*, 1951, 1020.
[7] *Idem*, *J.*, 1955, 3084.
[8] Lappert, *J.*, 1956, in the press.
[9] *Idem*, *J.*, 1953, 667.
[10] Edwards, Gerrard, and Lappert, *J.*, 1955, 1470.
[11] Lappert, *J.*, 1955, 784.
[12] Gerrard and Lappert, *J.*, 1951, 2545.
[13] *Idem*, *Chem. and Ind.*, 1952, 53.

pyridine (0·025 mole) to the ester (0·025 mole) at −70° to −40°. All the pyridine was withdrawn at 20°/0·2 mm. That pyridine and tri-(2 : 2 : 2-trichloroethyl) borate formed no complex was demonstrated in like manner. The *borate* (Found : Cl, 69·7; B, 2·3. $C_6H_4O_3Cl_9B$ requires Cl, 70·0; B, 2·4%), m. p. 97—98°, b. p. 112°/0·05 mm., was obtained in 64% yield from 2 : 2 : 2-trichloroethanol (23 g., 3 mols.) and boron trichloride (6·0 g., 1 mol.).

TABLE 1.

Alcohol	Yield (%) of ester [based on (2)]	B. p./mm.	n_D^{20}	Found : B (%)	Calc. : B (%)
Bu^nOH	83	96°/0·08	1·4748	4·7	4·6
Bu^iOH	85	75°/0·005	1·4719	4·7	4·6
Bu^sOH	87	71°/0·05	1·4675	4·75	4·6
Octan-2-ol	82	142—148°/0·1	1·4668	3·2	3·1

Pyridine (5·17 g., 3 mols.) was added to molten di-(2 : 2 : 2-trichloroethyl) phenylboronate (8·37 g., 1 mol.) at 60°. On cooling to 20°, a viscous liquid was obtained, which crystallised in 3 days. Unchanged pyridine was removed at 20°/0·2 mm. and after 8 hr. no further loss in weight occurred. The residue (9·93 g., 99%) was the 1 : 1 *compound* between pyridine and the boronate, m. p. 111—116° (Found : Cl, 45·3; C_5H_5N, 16·7. $C_{15}H_{14}O_3NCl_6B$ requires Cl, 45·9; C_5H_5N, 17·1%). The recovered pyridine had b. p. 115°, n_D^{20} 1·5073.

Hydrolysis of n-*Butyl* n-*Butylchloroboronite.*—To the ester (8·5 g., 1 mol.) at 0°, water (10·90 g., 1 mol.) was added during 1 hr. at 0°. A vigorous reaction occurred with evolution of hydrogen chloride and formation of a white precipitate. The mixture was shaken (2 hr.) whilst dry nitrogen was bubbled through it. Hydrogen chloride (1·8 g., 100%) was evolved and was absorbed in potassium hydroxide. On distillation a forerun (0·75 g.) of aqueous *n*-butanol, b. p. 35—40°/11 mm., was followed by di-*n*-butyl *n*-butylboronate (5·0 g., 100%), b. p. 109—111°/11 mm., which on redistillation had b. p. 103°/8 mm., n_D^7 1·4205, d_4^{20} 0·8308 (Found : B, 4·9. Calc. for $C_{12}H_{27}O_3B$: B, 5·1%). A higher-boiling fraction (0·70 g.) b. p. 115—119°/11 mm., slowly deposited a white solid (identified, after crystallisation from water, as boric acid). Yields are based on scheme (3).

n-*Butyl-alcoholysis of* n-*Butyl* n-*Butylchloroboronite.*—*n*-Butanol (1·26 g., 1 mol.) was added with shaking to the ester (3·00 g., 1 mol.) at 20°. Hydrogen chloride (0·60 g., 100%) was absorbed in potassium hydroxide. Distillation afforded di-*n*-butyl *n*-butylboronate (3·2 g., 88%), b. p. 112—115°/17 mm. (Found : B, 4·9%). Yields are based on scheme (4).

Interaction of Pyridine and n-*Butyl Phenylchloroboronite.*—The ester (6·75 g., 1 mol.) was added dropwise to pyridine (8·15 g., 3 mols.) at −10°. A white solid was formed and became molten at 0°. This was repeatedly extracted with *n*-pentane and then diethyl ether. A deliquescent solid (4·1 g.) (Found : Cl, 9·4; C_5H_5N, 37·2; B, 3·3%) remained. The pentane extract afforded pyridine (2·40 g., 0·9 mols.), b. p. 112°, n_D^{20} 1·5031 (Found : C_5H_5N, 97·8%), and an undistillable residue (0·5 g.). The ether extract, after removal of volatile matter (at 15°/0·3 mm. for 8 hr.), afforded the 1 : 2 *compound* between *n*-butyl phenylchloroboronite and pyridine (6·0 g., 49%) (Found : Cl, 10·05; C_5H_5N, 44·7. $C_{20}H_{24}ON_2ClB$ requires Cl, 10·0; C_5H_5N, 44·6%), which slowly (several days) lost pyridine at 15°/0·02 mm.

Interaction of n-*Butyl* n-*Butylchloroboronite and Pyridine.*—To the boronite (5·10 g., 2 mols.) at −70° was added pyridine (1·14 g., 1 mol.). The resulting oil solidified when kept at −70° for 7 days. This was thoroughly washed with *n*-pentane and filtered. The white, crystalline 1 : 1-*complex* between pyridine and *n*-butylboron dichloride (3·00 g., 96%), m. p. 77—81° (Found : Cl, 31·9; C_5H_5N, 38·3. $C_9H_{14}NCl_2B$ requires Cl, 33·2; C_5H_5N, 37·8%), was thus obtained. The pentane filtrate afforded di-*n*-butyl *n*-butylboronate (2·85 g., 93%), b. p. 104°/11 mm., n_D^{20} 1·4102 (Found : B, 4·6%). The yields are based on scheme (5).

Thermal Stability of n-*Butyl Phenylchloroboronite.*—To the ester (2·56 g.), anhydrous ferric chloride (0·0187 g.) was added at 20°. Within 10 min., the mixture set solid and became hot. After 1 hr. at 20°, volatile matter was removed at 10 mm. A condensate of *n*-butyl chloride (1·14 g., 95%), b. p. 76—79°/760 mm., n_D^{20} 1·4027, was collected and a white solid (1·48 g. Calc. for Ph·BO, 1·28 g.) remained. Yields are based on scheme (6).

The stability of the ester in the absence of a catalyst was determined by heating weighed samples in sealed tubes and analysing acidimetrically the mixture after arbitrary time intervals by hydrolysis with cold water (the chloroboronite, unlike *n*-butyl chloride, has chlorine which is readily hydrolysed by cold water). Results are shown in Table 2.

Thermal Stability of n-*Butyl* n-*Butylchloroboronite.*—When ferric chloride (0·0535 g.) was added to the ester (2·94 g.) at 20° an immediate heat of reaction was observed. After 10 min. at 20° volatile matter was removed at 10 mm., and *n*-butyl chloride (1·54 g., 100%), b. p. 77—79°/760 mm., n_D^{20} 1·4023, was collected at −80°. Ferric chloride was removed from the

TABLE 2.

Ester	Temp.	Time (hr.)	Decompn. (%)	Ester	Temp.	Time (hr.)	Decompn. (%)
Ph·BCl·OBu^n	100°	3	0	Bu^n·BCl·OBu^n	100°	1	0
,,	200	1	0	,,	200	1	4·5
,,	200	2½	4	,,	200	2½	23
,,	200	5	10	,,	200	5	43
,,	200	34	75	,,	200	24	92

residue (1·52 g.) by filtration and washing with ether. The filtrate afforded *n*-butylboron oxide (1·17 g., 84%), b. p. 130°/13 mm., n_D^{20} 1·4208 (Found: B, 12·8. Calc. for C_4H_9OB: B, 12·9%). Yields are based on scheme (6).

The stability of the ester in the absence of a catalyst was determined by the method described above. Results are shown in Table 2.

Catalytic Decomposition of 2-*Methylheptyl Phenylchloroboronite.*—To the chloroboronite (1·84 g.; α_D^{20} +30·0°), ferric chloride (0·05 g.) was added at 20°. The mixture was set aside for 12 hr., whereupon it set solid. Distillation afforded 2-chloro-octane (0·93 g., 94%), b. p. 60°/12 mm., α_D^{20} −10·5°, n_D^{20} 1·4272, and phenylboron oxide (0·84 g., 95%) was obtained from the solid residue. Yields are based on scheme (6).

Interaction of Pyridine and n-*Butyl Phenylfluoroboronite.*—Pyridine (1·45 g., 1·3 mols.) in *n*-pentane (20 c.c.) was added dropwise to the ester (2·60 g., 1 mol.) in *n*-pentane (10 c.c.) at 0°. The white precipitate which was instantly formed was filtered off and identified as the 1 : 1 *compound* between phenylboron difluoride and pyridine [1·50 g., 100% based on scheme (6)], m. p. 100—102° (Found: B, 5·7; C_5H_5N, 39·9. $C_{11}H_{10}NF_2B$ requires B, 5·3; C_5H_5N, 38·6%).

Interaction of Pyridine and n-*Butyl* n-*Butylfluoroboronite.*—To the boronite (4·35 g., 2 mols.) at −80° was added pyridine (1·08 g., 1 mol.). After 1 hr. at 20° there was a separation into two layers. The upper was di-*n*-butyl *n*-butylboronate (2·90 g., 99%), b. p. 90°/4 mm., n_D^{20} 1·4169 (Found: B, 5·0%), whilst the lower on distillation afforded the 1 : 1 *compound* between *n*-butylboron difluoride and pyridine (1·81 g., 72%), b. p. 74—76°/0·01 mm., n_D^{20} 1·4655 (Found: C_5H_5N, 42·1. $C_9H_{14}NBF_2$ requires C_5H_5N, 42·6%). Yields are based on a scheme analogous to (5).

The same products were obtained when the order of addition of the reagents was reversed.

Thermal Stability of n-*Butyl* n-*Butylfluoroboronite.*—When the freshly prepared ester (8·74 g.) was heated (5 hr.) under reflux at 80°/20 mm., *n*-butylboron difluoride (2·84 g., 98%), b. p. 34°/760 mm., n_D^{20} 1·3272 (Found: F, 35·3; B, 10·1. Calc. for $C_4H_9F_2B$: F, 35·8; B, 10·2%), was collected at −70°. The residue gave a forerun (0·85 g.), b. p. 68—110°/15 mm., n_D^{20} 1·3985, and di-*n*-butyl *n*-butylboronate (4·35 g., 74%), b. p. 110—112°/13 mm., n_D^{20} 1·4164 (Found: B, 5·0%). Yields are based on scheme (9).

Alcoholysis of Phenylboron Dichloride.—(a) *With* n-*butanol* (1 : 1). To the dichloride (4·45 g., 1 mol.) at 0° was added *n*-butanol (2·10 g., 1 mol.). The mixture was allowed to warm to 20° whilst through it a current of nitrogen was passed. Hydrogen chloride (0·98 g., 99%) was evolved and absorbed in potassium hydroxide. Distillation afforded *n*-butyl phenylchloroboronite (5·26 g., 96%) and a residue (0·20 g.). Yields are based on scheme (10).

(b) *With octan-2-ol* (1 : 1). The alcohol (1·66 g., 1 mol.; α_D^{20} + 5·62°) was added to the dichloride (2·03 g., 1 mol.) at −80°. Distillation afforded (+)-2-*methylheptyl phenylchloroboronite* (2·27 g., 70%), b. p. 94°/0·1 mm., α_D^{20} +29·5°, n_D^{20} 1·4865, d_4^{20} 0·965 (Found: Cl, 13·9; B, 4·4. $C_{14}H_{22}OClB$ requires Cl, 14·0; B, 4·3%).

(c) *With* tert.-*butanol* (1 : 2). The dichloride (3·60 g., 1 mol.) was added slowly to the alcohol (3·36 g., 2 mols.) at −80°, and the mixture was kept at −80° for ½ hr., whereupon a solid was formed; at 20°/6 mm., a condensate of *tert.*-butyl chloride [1·36 g., 33% based on scheme (13)], b. p. 50—51°/760 mm., n_D^{20} 1·3873, was collected and there was a pasty white residue (4·24 g.). This was washed with *n*-pentane and filtered off. The filtrate afforded di-*tert.*-butyl phenylboronate [2·62 g., 51% based on schemes (10) and (11)], b. p. 58—65°/0·5 mm., n_D^{20} 1·4650 (Found: B, 5·3%), and a solid remained.

(d) *With other alcohols* (1 : 2). The chosen alcohol (2 mols., usually on 0·05 molar scale) was

added slowly to phenylboron dichloride (1 mol.) at −80°. The loss in weight at 20 mm. corresponded to hydrogen chloride. Results are shown in Table 3.

TABLE 3. [Yields based on schemes (10) and (11)].

R in ROH	Yield (%) of HCl	Yield (%)	B. p./mm.	n_D^{20}	Found : B (%)	Calc. : B (%)
Bu^n	100	94	96°/0·02	1·4740	4·6	4·6
Bu^i	98	94	70°/0·02	1·4710	4·7	4·6
Bu^s	99	90	64°/0·02	1·4671	4·7	4·6
2-Methylheptyl	98	89	128°/0·2	1·4665	3·25	3·1
$(\alpha_D^{20} + 5{\cdot}62^5)$	$(\alpha_D^{20} +11{\cdot}28°)$					

(e) *With* n-*butanol in presence of pyridine.* To the alcohol (5·90 g., 2 mols.) and pyridine (6·20 g., 2 mols.) in chloroform (25 c.c.) at −70° was added dropwise, with shaking, phenylboron dichloride (6·20 g., 1 mol.) in chloroform (20 c.c.). The mixture was set aside for 12 hr. at 20°, whereafter the volatile matter was withdrawn at 15°/10 mm. *n*-Pentane was added and pyridinium chloride (8·00 g., 90%) (Found: Cl, 30·3; C_5H_5N, 66·6. Calc. for C_5H_6NCl: Cl, 30·7; C_5H_5N, 68·5%) was filtered off. The filtrate afforded di-*n*-butyl *n*-phenylboronate (9·00 g., 99%) which on redistillation had b. p. 72°/0·1 mm., n_D^{20} 1·4747, d_4^{20} 0·9245 (Found: B, 4·6%).

Interaction of the 1 : 1 *Complex between Phenylboron Dichloride* (1 *mol.*) *and Pyridine* (1 *mol.*) *with* n-*Butanol* (2 *mols.*).—(a) *At room temperature.* The complex (1·76 g., 1 mol.) was allowed to react with pyridine (0·583 g., 1 mol.) and *n*-butanol (1·094 g., 2 mols.) in chloroform (10 c.c.) at 20° for 12 hr., whereafter the solvent was removed at 20°/20 mm., *n*-pentane added and the mixture filtered. The filtrate, after evaporation at 20°/20 mm., left no residue.

(b) *In boiling chloroform.* The complex (1·92 g., 1 mol.), the alcohol (1·28 g., 2 mols.), and pyridine (0·635 g., 1 mol.) were heated under reflux in chloroform (15 c.c.) for 16 hr. The solvent was removed in a vacuum (20 mm.); *n*-pentane was added to separate pyridinium chloride (1·853 g., 98%) (Found: Cl, 30·4; C_5H_5N, 68·0%) which was precipitated, and di-*n*-butyl phenylboronate (1·54 g., 83%), b. p. 92°/0·3 mm., n_D^{20} 1·4750 (Found: B, 4·6%). Yields are based on scheme (13).

Interaction of n-*Butylboron Difluoride and Pyridine.*—Pyridine (2·88 g., 1 mol.) in *n*-pentane (10 c.c.) was added to the difluoride (3·88 g., 1 mol.) at −80°. The reaction was very vigorous and a white precipitate was formed instantly. After 1 hr. at 20°, the precipitate dissolved and two layers had separated. The pentane was removed at 0·1 mm. and the residue, a viscous, coloured oil, was the 1 : 1 *complex* (6·70 g., 99%), n_D^{20} 1·4651 (Found: C_5H_5N, 44·0%). This was distilled, then having b. p. 78°/0·01 mm., n_D^{20} 1·4665, d_4^{20} 1·075 (Found: C, 57·7; H, 7·7; C_5H_5N, 42·3. $C_9H_{14}NF_2B$ requires C, 58·4; H, 7·6; C_5H_5N, 42·6%).

In a separate experiment, the addition of the difluoride (1·26 g., 1 mol.) in *n*-pentane (10 c.c.) to pyridine (1·88 g., 2 mols.) at −80°, also afforded the 1 : 1 complex (1·82 g., 83%), b. p. 76—77°/0·01 mm., n_D^{20} 1·4670 (Found: C_5H_5N, 42·8%).

Interaction of Phenylboron Dichloride and Pyridine.—Pyridine (0·82 g., 1 mol.) in *n*-pentane (10 c.c.) was added to the dichloride (1·63 g., 1 mol.) in the same solvent (20 c.c.) at −80°. The white solid, which was instantly formed, was filtered off, washed with *n*-pentane, and freed from solvent at 15 mm. The 1 : 1 *complex* (2·45 g., 100%), m. p. 64° (opaque) (Found: Cl, 30·0; C_5H_5N, 34·1; B, 4·5. $C_{11}H_{10}NCl_2B$ requires Cl, 29·8; C_5H_5N, 33·2; B, 4·5%), was thus obtained

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309. *Nucleotides. Part XXXVI.* Adenosine-2′ Uridine-5′ Phosphate.*

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Adenosine-2′ uridine-5′ phosphate has been synthesised by condensing 3′ : 5′-di-*O*-acetyladenosine-2′ benzyl phosphorochloridate with 2′ : 3′-di-*O*-acetyluridine and subsequently removing protecting groups. The synthetic product showed the expected properties in both chemical and enzymic reactions. A convenient method for preparing 3′ : 5′-di-*O*-acetyladenosine by transacetylation is described.

Michelson and Todd [1] recently reported the first synthesis of a dinucleotide containing the 3′ : 5′-internucleotidic linkage characteristic of the natural nucleic acids. The synthetic compound (dithymidine dinucleotide) showed the same behaviour towards enzymes as the dinucleotides found in hydrolysates of natural deoxyribonucleic acids, thus providing valuable confirmation of the structural pattern of the latter. Clearly corresponding syntheses of diribonucleotides would be of at least equal value in the chemistry of ribonucleic acids, and, indeed, because of the ready availability of ribonucleosides as starting materials, preliminary although successful experiments on such syntheses were begun in these laboratories more than two years ago by Dr. R. H. Hall. As in the deoxyribonucleotide series, the first objective was the synthesis of a dinucleoside phosphate which would serve as a model for di- and higher poly-nucleotide syntheses. Diribonucleoside-5′ phosphates had already been prepared [2] but these were of little interest since there is good evidence that 5′ : 5′-internucleotidic linkages do not occur in ribonucleic acids; [2,3] only those containing 3′ : 5′- and 2′ : 5′-linkages were likely to give information of structural value.

The presence of the *cis*-α-glycol group in the ribonucleosides, *e.g.*, in adenosine (I) or uridine (II), complicates the synthesis of the diribonucleoside-2′ : 5′- and -3′ : 5′ phosphates in several ways. The only obvious method of unambiguous synthesis is the condensation of a suitably protected nucleoside, *e.g.*, (IV; U = uracil residue), with a protected nucleoside phosphorochloridate, *e.g.*, (III; A = adenine residue), or with a mixed anhydride of a protected nucleotide with some stronger acid. Phosphorochloridates in the ribonucleoside series are normally prepared by halogenation of the corresponding nucleoside benzyl phosphites, *i.e.*, they are nucleoside benzyl phosphorochloridates, and hence when they react with a nucleoside derivative the first product (*e.g.*, V) must be a triester of phosphoric acid. Such a compound can have reasonable stability only if there is no free hydroxyl group in either nucleoside residue adjacent to the point of attachment of the phosphate group.[4] In other words, with this type of synthesis, complete removal of the benzyl residue before there is any loss of other protecting groups is essential; moreover, the protecting groups on the nucleosides must be such that they can subsequently be removed under conditions which avoid hydrolytic breakdown of the labile dinucleotide structure (VI).

3′ : 5′-Di-*O*-acetyladenosine has been prepared by Brown, Fasman, Magrath, and Todd [5] by partial acetylation of 5′-*O*-acetyladenosine. This method was not very convenient for large-scale preparation but a satisfactory alternative was found employing the principle of transacetylation. 2′ : 3′ : 5′-Tri-*O*-acetyladenosine is readily accessible and from it by partial hydrolysis 5′-*O*-acetyladenosine. When these two compounds, carefully dried, are mixed in equimolecular proportion and heated just above the melting point of the mixture transacetylation occurs. Working up the product by countercurrent distribution gives 3′ : 5′-di-*O*-acetyladenosine in good yield in addition to some unchanged starting

* Part XXXV, *J.*, 1956, 1371.

[1] Michelson and Todd, *J.*, 1955, 2632. In this paper, *J.*, 1955, 2637, line 27; *for* water (9 c.c.), and 0·4N-sulphuric acid (4·5 c.c.), then *read* water (90 c.c.), and 0·4N-sulphuric acid (4·5 c.c.), for 1 hr. then.

[2] Elmore and Todd, *J.*, 1952, 3681.

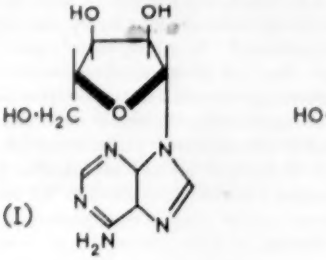
[3] Brown and Todd, *J.*, 1952, 52.

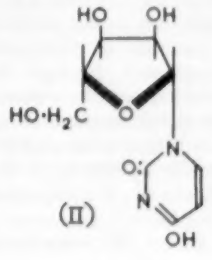
[4] Brown, Magrath, and Todd, *J.*, 1954, 1442.

[5] Brown, Fasman, Magrath, and Todd, *J.*, 1954, 1448.

materials which can be re-processed. It is of interest that neither by this method nor by partial acetylation have we ever isolated any 2′ : 5′-di-*O*-acetyladenosine. Whether this is due to selective acetylation at $C_{(3')}$ or to migration of the acetyl group from $C_{(2')}$ to $C_{(3')}$ during the prolonged countercurrent distribution process in aqueous media is still an open question; only one spot corresponding to a diacetyladenosine is observed on paper chromatography of the crude product obtained by either method, but in the absence of a pure reference sample of 2′ : 5′-di-*O*-acetyladenosine it is difficult to assess the value of this observation.

The fusion method of preparation having made 3′ : 5′-di-*O*-acetyladenosine an accessible starting material it was decided to use it in attempts to prepare a dinucleoside-2′ : 5′-


(I)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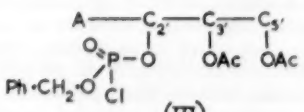
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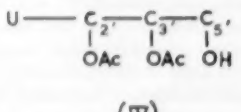
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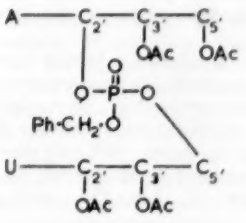
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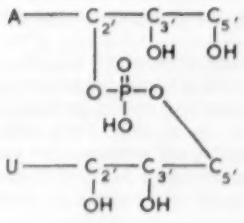

(VI)

phosphate. 3′ : 5′-Di-*O*-acetyladenosine-2′ benzyl phosphate [5] was chosen as an appropriate model for an acetylated dinucleoside phosphate in hydrolysis experiments; it was found that removal of acetyl groups without affecting the benzyl group was best effected by cold aqueous barium hydroxide at pH 9·6.

3′ : 5′-Di-*O*-acetyladenosine was converted *via* 3′ : 5′-di-*O*-acetyladenosine-2′ benzyl phosphite into 3′ : 5′-di-*O*-acetyladenosine-2′ benzyl phosphorochloridate [6] (III) which was not isolated but was prepared in solution as required and used immediately. With anhydrous 2′ : 3′-di-*O*-acetyluridine [6] (IV) at room temperature in presence of dry 2 : 6-lutidine, this gave a complex mixture, which was hydrogenated in presence of acetic acid to remove the benzyl group, then deacetylated and subjected to anion-exchange chromatography on Dowex 2 resin (formate form). Adenosine-2′ uridine-5′ phosphate (VI) was eluted with 0·05N-formic acid and crystallised from aqueous ethanol in colourless needles. The dinucleoside phosphate showed all the properties predicted on the basis of the known behaviour of simple nucleotide monoesters and ribonucleic acids. With 0·1N-aqueous sodium hydroxide at 37° it yielded uridine and a mixture of adenosine-2′ and adenosine-3′

[6] Kenner, Todd, Webb, and Weymouth, *J.*, 1954, 2288.

phosphate. Purified snake-venom diesterase hydrolysed it to uridine-5′ phosphate and adenosine[7] (Calculated molar ratio, 1 : 1; found, 1·2 : 1). Pancreatic ribonuclease had no action on the substance (absence of $C_{(3')}$ linkage on the pyrimidine nucleoside residue),[8] nor was it affected by spleen 3′-diesterase.[9] Periodate oxidation followed by incubation at pH 10 in a glycine buffer for 18 hours gave uracil and adenosine-2′ phosphate.[10,11] We are indebted to Dr. L. A. Heppel for his kindness in carrying out the enzyme experiments on the synthetic material.

The yield of adenosine-2′ uridine-5′ phosphate obtained, even with vigorous drying of all starting materials and solvents, was low (*ca.* 8%). After its removal from the ion-exchange column further elution gave mainly a mixture of adenosine-2′ and -3′ phosphate, followed by a more firmly held but rather unstable material which, by analogy with the observations made in the synthesis of dithymidine-3′ : 5′ phosphate,[1] may have been P^1P^2-diadenosine-2′ pyrophosphate. Whether the low yield of dinucleoside phosphate is due to lack of reactivity in either one of the starting materials or to preferential formation of large amounts of unstable pyrophosphate is uncertain; in either case the major end products would be adenosine-2′ and adenosine-3′ phosphate. It is, however, clear that synthesis of a 2′ : 5′-dinucleotide by this type of method should be feasible and there is every reason to expect that the 3′ : 5′-compound should be accessible by an analogous procedure.

Experimental

5′-O-Acetyladenosine by Partial Hydrolysis of 2′ : 3′ : 5′-Tri-O-acetyladenosine.—Methanolic ammonia (120 c.c., saturated at 0°) was added to a solution of 2′ : 3′ : 5′-tri-*O*-acetyladenosine (12 g.) in ethanol (1300 c.c.) and the mixture kept at room temperature for 45 min. Solvent was removed under reduced pressure, water (250 c.c.) was added to the residue, and the aqueous solution extracted once with chloroform (the chloroform extract gave on evaporation 3 g. of unchanged triacetyladenosine) and taken to half volume under reduced pressure. The solution was kept at 0° overnight, whereupon 5′-*O*-acetyladenosine (4 g.) separated as needles, m. p. and mixed m. p. 135°.

Paper-chromatographic examination of the crude product from the above experiment showed no formation of diacetyl- or of other monacetyl-adenosine; the only other product was free adenosine.

3′ : 5′-Di-O-acetyladenosine.—(a) *By partial acetylation.* Partial acetylation[5] of 5′-*O*-acetyladenosine (24 g.) and separation of the products by countercurrent distribution (100 transfers; ethyl acetate–water) gave 5′-*O*-acetyladenosine (7 g.; m. p. 135°), 3′ : 5′-di-*O*-acetyladenosine (8·5 g.; m. p. 169—170°), and 2′ : 3′ : 5′-tri-*O*-acetyladenosine (7·4 g.; m. p. 168°). Recrystallised first from acetone–light petroleum (b. p. 60—80°) and then from ethanol–light petroleum (b. p. 60—80°) 3′ : 5′-di-*O*-acetyladenosine formed needles, m. p. 170° (Found, in material dried at 105°/10^{-3} mm.: C, 48·1; H, 5·0; N, 19·6. Calc. for $C_{14}H_{17}O_6N_5$: C, 47·9; N, 19·9%).

(b) *By trans-acetylation.* A finely ground mixture of anhydrous 5′-*O*-acetyladenosine (6·9 g.) and 2′ : 3′ : 5′-tri-*O*-acetyladenosine (10 g.) was heated under reduced pressure to 160° for 5 min. to ensure complete melting, then kept *in vacuo* in a closed system at 130° for 12 hr. The cooled melt was shown to contain mono-, di-, and tri-*O*-acetyladenosine by paper chromatography, and it was subjected to countercurrent distribution in an automatically operated machine (20 c.c. phases; 100 transfers; ethyl acetate–water). This yielded 5′-*O*-acetyladenosine (tubes 3—25; 3·4 g.; m. p. 135°), 3′ : 5′-di-*O*-acetyladenosine (tubes 33—63; 7·5 g.; a glass), and 2′ : 3′ : 5′-tri-*O*-acetyladenosine (tubes 75—93; 4·5 g.; m. p. 168°). The 3′ : 5′-di-*O*-acetyladenosine was recrystallised as described under (a) above and had m. p. 170°; further recrystallisation from water raised the m. p. to 172—173° (yield 6 g.) (Found, in material dried at 105°/10^{-3} mm.: C, 47·7; H, 5·1; N, 19·7%).

Adenosine-2′ Uridine-5′ Phosphate.—*N*-Chlorosuccinimide (0·682 g.) was added to a solution of 3′ : 5′-di-*O*-acetyladenosine-2′ benzyl phosphite[6] (2·13 g.) in dry benzene (15 c.c.) and the mixture kept at room temperature for 4 hr. Anhydrous 2′ : 3′-di-*O*-acetyluridine[6] (1·26 g.) was then added, followed by 2 : 6-lutidine (2·5 c.c.) and acetonitrile (50 c.c.), and the mixture was

[7] Cohn and Volkin, *J. Biol. Chem.*, 1953, **203**, 319.
[8] Brown and Todd, *J.*, 1953, 2040.
[9] Brown, Heppel, and Hilmoe, *J.*, 1954, 40.
[10] Brown, Fried, and Todd, *J.*, 1955, 2206.
[11] Whitfield and Markham, *Nature*, 1953, **171**, 1151.

shaken at room temperature till it formed a clear solution (*ca.* 2 hr.), then set aside for 36 hr. at 25°. Solvent was removed under reduced pressure at room temperature and the residue freed from traces of lutidine *in vacuo* over phosphoric oxide. The product was next dissolved in aqueous ethanol (30 c.c. of 65%), glacial acetic acid (1 c.c.) was added, and the solution hydrogenated at room temperature and atmospheric pressure with a palladium oxide catalyst. Catalyst was filtered off and aqueous barium hydroxide added to pH 9·6. The solution was maintained at this pH by cautious addition of barium hydroxide during 2 days at room temperature and then put through a column of Dowex 2 resin (formate form; 9 × 3·5 cm.), the column being well washed with water. *Adenosine-2′ uridine-5′ phosphate* was eluted with 0·05N-formic acid, an automatic fraction-collector being used. Appropriate fractions were pooled, concentrated to small bulk under reduced pressure, and freeze-dried. The residue recrystallised from aqueous ethanol, giving the dinucleoside phosphate as colourless needles, (250 mg.), m. p. 175—180° (decomp.) (Found, in air-dried material: C, 36·5; H, 4·7; N, 15·5; loss in wt. at 70°/1 mm. during 10 hr., 9·2. $C_{19}H_{24}O_{12}N_7P,3H_2O$ requires C, 36·4; H, 4·8; N, 15·6; loss on drying, 8·6. Found, in anhyd. material: P, 5·4. $C_{19}H_{24}O_{12}N_7P$ requires P, 5·4%). R_F values (Whatman No. 1 paper) were (*a*) 0·3 in *n*-butanol–acetic acid–water (5 : 2 : 3), (*b*) 0·39 in 95% ethanol–M-ammonium acetate (75 : 30), (*c*) 0·62 in propan-1-ol–ammonia–water (6 : 3 : 1), (*d*) 0·18 in propan-2-ol–ammonia–water (7 : 1 : 2), and (*e*) 0·57 in propan-2-ol–1%-ammonium sulphate (3 : 2).

Grateful acknowledgment is made to the Rockefeller Foundation for its support. One of us (L. S.) took part in this work while on leave from the Centre national de la Recherche scientifique, France.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 30th*, 1955.]

310. *A Study of Melanin Formation by Use of* 2-(3 : 4-*Dihydroxy*-[3-^{14}C]*phenyl*)-, 2-(3 : 4-*Dihydroxy*[4-^{14}C]*phenyl*)-, *and* 2-(3 : 4-*Dihydroxy*[5-^{14}C]*phenyl*)-*ethylamine.*

By G. A. SWAN and D. WRIGHT.

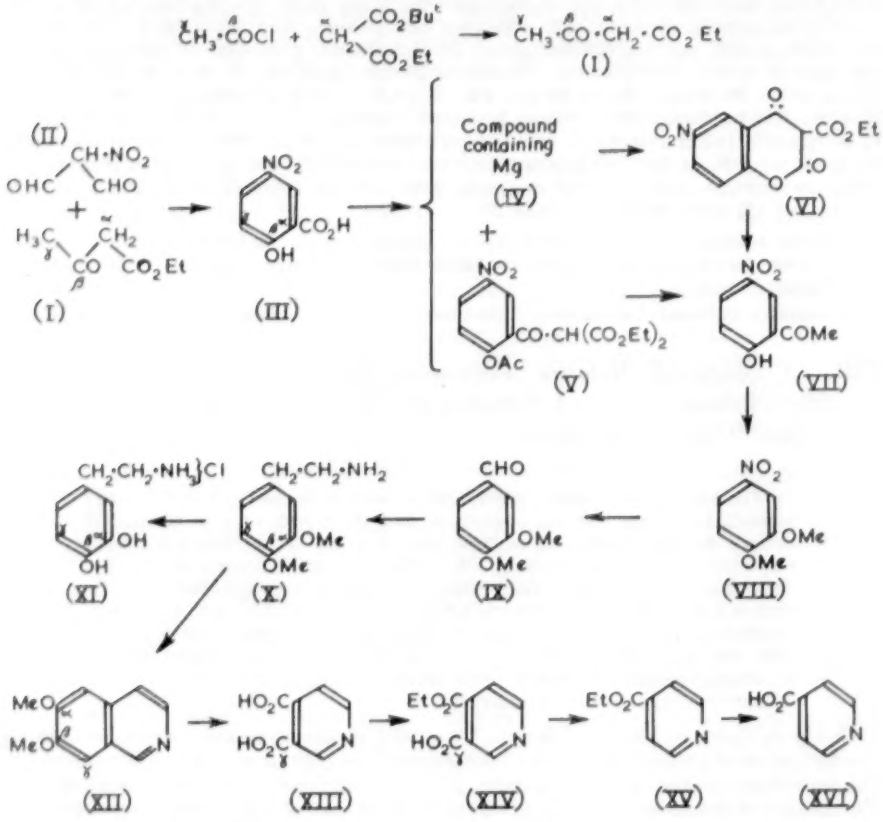
The compounds named in the title have been synthesised and used to study melanin formation. It was found that 29·8, 27·2, and 3·5% of the carbon dioxide evolved during the reaction arise from the 3-, 4-, and 5-positions, respectively of the benzene ring. A comparison of the specific activities of the melanins with those of their precursors suggests that approximately one unit in five in the polymer has undergone oxidative fission, with the loss of (probably) $C_{(4)}$, $C_{(5)}$, and $C_{(6)}$ of the indole nucleus. The results are in keeping with the structure of melanin suggested by Bu'Lock and Harley-Mason [1] (involving coupling of indole units between positions 3 and 7), with this oxidation occurring as a side-reaction.

IT has been shown by Swan and Wright [2] that 96% of the carbon dioxide evolved during the formation of melanin from 2-(3 : 4-dihydroxyphenyl)ethylamine (cf. XI) originates in the breakdown of the benzene nucleus. No conclusion was, however, drawn regarding the relation of the specific activity of the melanin to that of the original amine, since the increases observed were only of the same order as the possible experimental error. If nearly all the evolved carbon dioxide arose from one particular carbon atom, and the experiment were made with 2-(3 : 4-dihydroxyphenyl)ethylamine labelled specifically with ^{14}C at that position, then the specific activity of the evolved carbon dioxide should be nearly eight times as great as that formed by combustion of the amine. Moreover, the activity of the resulting melanin should be considerably lower than that of the amine, provided that the molecules undergoing loss of carbon dioxide were in fact incorporated in or into the melanin. The use of specifically labelled compounds should therefore provide a test of the validity of the postulates put forward by Bruce [3] and Jolles,[4] in both of which the oxidative fission of the benzene nucleus is regarded as an essential step in

[1] Bu'Lock and Harley-Mason, *J.*, 1951, 703.
[2] Swan and Wright, *J.*, 1954, 381.
[3] Bruce, *Chem. and Ind.*, 1954, 310; *J. Appl. Chem.*, 1954, **4**, 469.
[4] Jolles, *Chem. and Ind.*, 1953, 845, 1367.

melanin formation. In our earlier work, we carried out our radioactivity measurements on " infinitely thick " layers of barium carbonate. In the experiments described in this paper, all measurements were made by the gas-counting method on carbon dioxide, which has led to some increase in accuracy and has enabled us to use compounds of much lower specific activity (approximately 0·2 μC/mmole).

In the course of experiments designed to introduce ^{14}C into a specific position of the benzene ring the condensation of acetone or ethyl acetoacetate with various malondialdehydes was investigated. In the case of ethoxycarbonylmalondialdehyde (cf. Prelog,



Würsch, and Königsbacher [5]) and cyanomalondialdehyde no condensation products could be isolated under a variety of conditions; and only a small yield of *p*-nitrophenol was obtained from acetone and nitromalondialdehyde (II) (cf. Hill and Torray [6]). Also benzoylacetone and acetylacetone failed to give the expected hydroxy-benzophenone or -acetophenone derivatives. However an almost quantitative yield of 5-nitrosalicylic acid (III) was obtained from the condensation of ethyl acetoacetate and nitromalondialdehyde and this was converted into 2-(3 : 4-dihydroxyphenyl)ethylamine in an eleven-stage synthesis. The acetylated acid chloride when condensed with ethoxymagnesium malonic ester gave two compounds (IV and V) both of which could be hydrolysed to 2-hydroxy-5-nitroacetophenone (VII) : one was presumably the benzoylmalonate derivative (V), while the other

[5] Prelog, Würsch, and Königsbacher, *Helv. Chim. Acta*, 1951, **34**, 258.
[6] Hill and Torray, *Ber.*, 1895, **28**, 2597.
[7] Anschütz, *Annalen*, 1909, **367**, 169.

appeared to be a magnesium derivative (IV) of ethyl 3 : 4-dihydro-6-nitro-4-oxocoumarin-3-carboxylate. (Anschütz [7] obtained ethyl 3 : 4-dihydro-4-oxocoumarin-3-carboxylate by reaction between 3 mols. of sodiomalonic ester and 1 mol. of acetylsalicyloyl chloride.) The above 2-hydroxy-5-nitroacetophenone could also be obtained from 5-nitrosalicylic acid by initially methylating the hydroxyl group, but the overall yield was lower. 4-Nitrocatechol was obtained in high yield from 2-hydroxy-5-nitroacetophenone by Dakin's method,[8] and methylation (to VIII) and reduction afforded 4-aminoveratrole. Several attempts to convert 4-aminoveratrole *via* 4-cyanoveratrole into veratraldehyde (IX) by application of Stephen's method [9] were unsuccessful. However by treatment of the diazonium compound with formaldoxime according to Beech's method [10] a 50% yield of veratraldehyde was obtained. An attempted preparation of 4-methoxybenzoylnitromethane by the application of Beech's method to methazonic acid gave only an azo-compound (cf. Kimich [11]). Veratraldehyde was then converted into 2-(3 : 4-dihydroxyphenyl)ethylamine (*via* X) as described by Swan and Wright.[2]

Thus by initially preparing ethyl acetoacetate (I) labelled in the α-, β-, and γ-position, specimens of 2-(3 : 4-dihydroxyphenyl)ethylamine hydrochloride (XI) were obtained labelled in the 3-, 4-, and 5-nuclear positions respectively. The radiochemical yields (from barium carbonate to dihydroxyphenylethylamine hydrochloride) achieved were 0·4, 1·3, and 1·1%, respectively. The results obtained when each of these compounds was converted into melanin are summarised in Table 1.

TABLE 1.

	Weight (mg.)		Radioactivity (as CO_2) (counts/min.)	
	(1)	(2)	(1)	(2)
2-(3 : 4-Dihydroxy[3-^{14}C]phenyl)ethylamine hydrochloride	72·2	76·4	1259	1259
$BaCO_3$ resulting from melanin formation	19·1	21·0	3010	2980
Melanin	23·8	22·5	1125	1132
Melanin (refluxed for 24 hr. with 2N-HCl)	—	—	1044	1070
2-(3 : 4-Dihydroxy[4-^{14}C]phenyl)ethylamine hydrochloride	71·9	71·9	1377	1377
$BaCO_3$ resulting from melanin formation	22·6	20·1	2830	3150
Melanin	29·0	25·06	1250	1282
Melanin (refluxed for 24 hr. with 2N-HCl)	—	—	1210	1160
2-(3 : 4-Dihydroxy[5-^{14}C]phenyl)ethylamine hydrochloride	76·0	72·9	498	498
$BaCO_3$ resulting from melanin formation	21·2	21·1	141	137
Melanin	27·8	26·0	510	505
Melanin (refluxed for 24 hr. with 2N-HCl)	—	—	518	510

That these compounds were truly specifically labelled was demonstrated by the conversion of some of the radioactive 2-(3 : 4-dimethoxyphenyl)ethylamine from each synthesis into 6 : 7-dimethoxy*iso*quinoline (XII), and the three specimens of the *iso*-quinoline [12] were then oxidised to cinchomeronic acid (XIII). The cinchomeronic acid obtained from two of the samples of *iso*quinoline, *i.e.*, those synthesised from 2-(3 : 4-dimethoxy[3-^{14}C]phenyl)- and 2-(3 : 4-dimethoxy[4-^{14}C]phenyl)-ethylamine, were completely inactive whereas in the case of the cinchomeronic acid obtained from 2-(3 : 4-dimethoxy[5-^{14}C]phenyl)ethylamine all of the radioactivity was retained in the acid. As expected, this radioactivity was completely lost during the conversion [13] of the cinchomeronic acid into *iso*nicotinic acid (XVI) *via* the silver salt of 4-ethyl hydrogen cinchomeronate (XIV). These results (Table 2) show that no appreciable rearrangement had occurred at any stage of the syntheses, provided one makes the plausible assumption that interchange of $C_{(3)}$ and $C_{(4)}$ of the benzene nucleus does not occur.

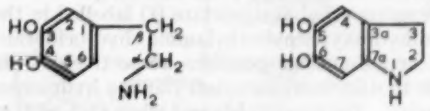
From the results given in Table 1 it can be calculated that 29·8, 27·2, and 3·5% of the evolved carbon dioxide originates in the 3-, 4-, and 5-position, respectively, of the 2-(3 : 4-dihydroxyphenyl)ethylamine. We have already shown [2] that 1·9 and 2·3% of the carbon dioxide originates in the α- and the β-position of the side chain, respectively. We therefore

[8] Dakin, *Amer. Chem. J.*, 1909, **42**, 477.
[9] Stephen, *J.*, 1925, 1874.
[10] Beech, *J.*, 1954, 1297.
[11] Kimich, *Ber.*, 1877, **10**, 146.
[12] Späth and Polgar, *Sitzungsber. Akad. Wiss. Wien*, 1928, **137**, IIb, 1142.
[13] Strache, *ibid.*, 1890, **99**, IIb, 153.

TABLE 2.

	Radioactivity (as CO_2) (counts/min.)				
	6 : 7-Dimethoxy*iso*quinoline	Cinchomeronic acid Calc.	Found	*iso*Nicotinic acid Calc.	Found
[6-^{14}C]	763	0	2	—	—
[7-^{14}C]	1225	0	5	—	—
[8-^{14}C]	1136	1785	1770	0	2

infer that 35·3% arises from positions 1, 2, and 6 together. Assuming cyclisation to 5 : 6-dihydroxyindole to occur, it seems likely that only something of the order of 2% will arise from each of positions 1 and 6. (As two carbon atoms of the pyrrole ring remain intact, it appears probable that the entire pyrrole ring will remain unbroken; the small evolution of carbon dioxide from positions α, β, 1, 5, and 6 might be due to complete oxidation of a small amount of the amine.) This would imply that something of the order of 30% would originate from the 2-position. Unfortunately we have not yet proved this,



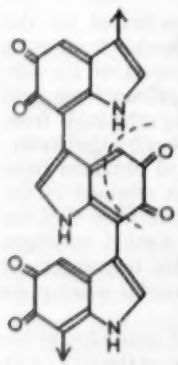
because the above synthesis is unsuited to the preparation of the required 2-(3 : 4-dihydroxy[2-^{14}C]phenyl)ethylamine—although it is hoped to do so later. However, if these figures are tentatively accepted, they would correspond in the case of 5 : 6-di-hydroxyindole to the results in Table 3.

TABLE 3.

Position in 5 : 6-dihydroxyindole ...	2	3	3*a*	4	5	6	7	7*a*
% of total evolved CO_2	1·9	2·3	*ca.* 2 *	*ca.* 30 *	29·8	27·2	3·5	*ca.* 2 *

* Values marked thus have not been measured directly; they are merely approximate, hypothetical values.

These results could be readily explained on the basis of a polyindolequinone structure for melanin, involving linkage between the 3- and the 7-position: this was postulated by Bu'Lock and Harley-Mason [1] (cf. Horner and Spietschka [14]), and received support from the oxygen-uptake experiments and spectroscopic determinations on various alkylated dihydroxyindoles by Beer, Broadhurst, and Robertson,[15] although certain observations conflict with the similar experiments of Cromartie and Harley-Mason.[16] We have already put forward evidence that the evolution of carbon dioxide during the melanin formation is a side-reaction, due to the action of hydrogen peroxide which is formed during the primary reactions. It seems likely that the action of this hydrogen peroxide might be to split the linkage between positions 5 and 6 of the polyindolequinone, thus converting $C_{(5)}$ and $C_{(6)}$ into carboxyl groups. If these quinone residues are linked between positions 3 and 7, this oxidation might continue to position 4, and decarboxylation might result in the splitting off of $C_{(4)}$, $C_{(5)}$, and $C_{(6)}$ in some of the units (cf. *A*). However, as $C_{(7)}$ is involved in the polymeric linkage, it could not split off without the polymer's breaking down to smaller units.



(*A*)

The fact that the 2-(3 : 4-dihydroxyphenyl)ethylamine molecules which undergo loss of carbon dioxide are in fact incorporated in or into the melanin follows from a comparison of the specific activities of the carbon dioxide formed by combustion of the melanins and of the original amine hydrochlorides (Table 1). Also, the relative amounts of carbon dioxide arising from the different positions suggest that oxidation occurs mainly after, rather than before, cyclisation and polymerisation.

When the melanins were boiled for 16 hr. with dilute hydrochloric acid, they underwent some loss in weight (*ca.* 15%), a slight increase in carbon content and a slight change in

[14] Horner and Spietschka, *Annalen*, 1955, **591**, 1.
[15] Beer, Broadhurst, and Robertson, *J.*, 1954, 1947.
[16] Cromartie and Harley-Mason, *Chem. and Ind.*, 1953, 972.

specific activity. Longer boiling, however, appeared to bring about little further change (see Table 4). In the following considerations, the specific activities of the melanin samples which have been boiled for 24 hr. with acid are therefore used. Evaporation of the acid extract yielded a dark brown, gummy residue, which dissolved readily in water to give a solution which gave a dark precipitate when neutralised with ammonia.

TABLE 4

Compound	Radioactivity (counts/min.) of CO_2 produced on combustion
2-(3 : 4-Dihydroxy[4-^{14}C]phenyl)ethylamine hydrochloride	1320
Melanin (not refluxed)	1220
Melanin (refluxed for 3 hr. with 2N-HCl)	1167
" (" 24 hr. ")	1146
" (" 72 hr. ")	1140

The specific activities of the " purified " melanins can be explained if it is assumed that one indole unit in five in the polymer loses carbon from positions 4, 5, and 6. This would require the melanins obtained from 2-(3 : 4-dihydroxy[3-^{14}C]phenyl)- and 2-(3 : 4-dihydroxy[4-^{14}C]phenyl)-ethylamine to have 86·5% of the radioactivity of the corresponding amine hydrochlorides. The activities actually observed were 84 and 86·8%, respectively. In the case of 2-(3 : 4-dihydroxy[5-^{14}C]phenyl)ethylamine, the evolved carbon dioxide is of low specific activity, and the melanin formed, on combustion, yields carbon dioxide of slightly higher activity than that derived by burning the amine hydrochloride. The latter fact is in keeping with linkage at the 7-position of the indole nucleus.

It would be interesting to repeat the above experiments on the formation of melanin from the labelled precursors in the presence of catalase and of hydrogen peroxide. However, it is clear that the fission of the benzene ring, with evolution of carbon dioxide, should be regarded as a side-reaction, not an essential step in the primary formation of melanin, as suggested by Bruce[3] and by Jolles.[4]

EXPERIMENTAL

The radioactivity determinations were carried out as described by Swan,[17] and the oxidation of 2-(3 : 4-dihydroxyphenyl)ethylamine to melanin as described by Clemo, Duxbury, and Swan.[18]

Ethyl [α-^{14}C], [β-^{14}C], *and* [γ-^{14}C]*Acetoacetate* (I).—[*Me*-^{14}C]Acetic acid was prepared from [^{14}C]methyl iodide by the method of Cox, Turner, and Warne[19] and [*carboxy*-^{14}C]acetic acid by that of Lemmon.[20] Each was converted into [^{14}C]acetyl chloride as described by Cox and Turner.[21]

Specimens of ethyl acetoacetate labelled in the α-, β-, and γ-position respectively were all prepared by condensation of acetyl chloride with *tert.*-butyl ethyl malonate (one or other being appropriately labelled) as described for ethyl [β-^{14}C]acetoacetate by Dauben and Bradlow.[22] Small amounts of ethyl acetoacetate were present in the benzene distillate; these were recovered by washing it with sodium hydroxide solution, the extract being used in a subsequent condensation with nitromalondialdehyde. Considerable amounts (*ca.* 20%) of acetylmalonic ester (b. p. 110—115°/14 mm.) remained after the distillation of the ethyl acetoacetate. The 2 : 4-dinitrophenylhydrazone of the former was obtained from ethanol as yellow needles, m. p. and mixed m. p. 144—145° (Found: C, 47·4; H, 4·95; N, 14·55. Calc. for $C_{15}H_{18}O_8N_4$: C, 47·1; H, 4·7; N, 14·65%).

Attempts to convert acetylmalonic ester into ethyl acetoacetate following the general methods of Riegel and Lilienfeld,[23] Eisner, Elvidge, and Linstead,[24] and Brändström[25] were unsuccessful.

Diethyl [α-^{14}C]*Malonate*.—This was required for the preparation of ethyl [α-^{14}C]acetoacetate.

[17] Swan, *J.*, 1955, 1039.
[18] Clemo, Duxbury, and Swan, *J.*, 1952, 3464.
[19] Cox, Turner, and Warne, *J.*, 1950, 3167.
[20] Lemmon, in " Isotopic-Carbon " by Calvin, Heidelberger, Reid, Tolbert, and Yankwich, Chapman and Hall, London, 1949, p. 178.
[21] Cox and Turner, *J.*, 1950, 3176.
[22] Dauben and Bradlow, *J. Amer. Chem. Soc.*, 1952, **74**, 5204.
[23] Riegel and Lilienfeld, *ibid.*, 1945, **67**, 1273.
[24] Eisner, Elvidge, and Linstead, *J.*, 1950, 2223.
[25] Brändström, *Acta Chem. Scand.*, 1951, **5**, 820, 1413.

A solution of potassium cyanoacetate, prepared from [*Me*-^{14}C]acetic acid (4 g.) by Ropp's procedure,[26] was evaporated to dryness and was refluxed for 1 hr. with ethanol (14 ml.) and sulphuric acid (10 ml.; *d* 1·84). Water was then added, and the ester was extracted with ether and distilled (4·75 g., 45%).

This ester was converted into *tert.*-butyl ethyl [α-^{14}C]malonate by the method of Breslow, Baumgarten, and Hauser.[27] The conversion of diethyl [α-^{14}C]- into ethyl hydrogen [α-^{14}C]-malonate was carried out in two runs since the average chemical yield over the two stages was only *ca.* 60%. The above diethyl [α-^{14}C]malonate (4·75 g.) was diluted with inactive material (5·25 g.) and converted into ethyl hydrogen [α-^{14}C]malonate as described by Breslow *et al.*[27] From this first run, the mother-liquors from which the monopotassium salt had crystallised and also those from the extraction of the half ester were taken to dryness. The residue was then refluxed for 2 hr. with sulphuric acid (5 ml.; *d* 1·84), ethanol (10 ml.), and diethyl malonate (6 g.). Water was added and the ester was extracted, distilled (10·1 g.), and again converted into ethyl hydrogen [α-^{14}C]malonate. By this process a greater radiochemical yield was obtained.

5-Nitrosalicyclic Acid (III).—This was prepared by Hill's method.[28] Ethyl acetoacetate (5·65 g.) and sodium nitromalondialdehyde monohydrate (8·55 g., 1·3 mols.) were added to a mixture of 10% sodium hydroxide solution (21·5 ml.) and water (68 ml.). The resulting solution was kept for 4 days at room temperature and then acidified, giving the acid (7·55 g., 95%; m. p. 223—224°). When only 1 mol. of nitromalondialdehyde was used the yield was 65%. An equally good yield of 5-nitrosalicyclic acid was obtained by first allowing the ethyl aceto-acetate to stand with sodium hydroxide solution (1 mol.) for 24 hr. before the addition of the nitromalondialdehyde. This suggests that hydrolysis occurs before condensation.

Methyl 2-Methoxy-5-nitrobenzoate.—5-Nitrosalicyclic acid is difficult to methylate (Simonsen and Rau [29]). Thus, refluxing 5-nitrosalicyclic acid with 6 mols. of dimethyl sulphate in dry toluene for 10 hr. in the presence of excess of sodium hydrogen carbonate (cf. Clemo and Swan [30]) gave mainly methyl 5-nitrosalicylate and 12% of dimethylated material.

Complete methylation was effected by using diazomethane (0·625 g., 2·5 mols.) in ether (50 ml.) with 5-nitrosalicyclic acid (1 g.) in ether at 0° for 2 days. The crystals (0·5 g.; m. p. 100°) were then collected and the filtrate on evaporation gave a further 0·6 g., m. p. 98°.

2-Methoxy-5-nitrobenzoic Acid.—The methyl ester (0·5 g.) was boiled for 5—10 min. with sodium hydroxide solution (10%; 5 ml.), and the resulting solution was cooled and acidified, giving the acid (0·45 g.; m. p. 148°).

2-Acetoxy-5-nitrobenzoic Acid.—This was prepared by the method of Grimme and Schmitz [31] in 96% yield.

2-Acetoxy-5-nitrobenzoyl Chloride.—The acid (7·65 g.) was vigorously stirred at 80° with thionyl chloride (13·5 ml.) in benzene (27 ml.). After 1—2 hr. dissolution was complete; the thionyl chloride was removed and the residue distilled in a short-path still [90%; b. p. 150° (bath)/0·01 mm.]. In the isotopic synthesis inactive "chaser" (0·35 g.) was used; the yield of acid chloride was then 7·6 g. (cf. Grimme and Schmitz [31]).

Ethyl 2-Acetoxy-5-nitrobenzoylmalonate (V).—Magnesium (0·93 g.) was treated with dry ethanol (5·3 ml.), diethyl malonate (6·9 g.), and carbon tetrachloride (0·15 ml.). When reaction slackened, ether (27 ml.) was added and the whole was refluxed for 1 hr., all the magnesium dissolving. The above acid chloride (7·6 g.) in benzene (28 ml.) was added dropwise with stirring during 5 min. and, after being warmed for 2 hr. and then cooled, the solution was treated with water (30 ml.). The mixture was stirred for 5 min. and then shaken with chloroform (60 ml.). After removal of some insoluble by-product, the chloroform was separated and the aqueous portion extracted with more chloroform (50 ml.). The combined washings were dried (Na_2SO_4), and the solvent was evaporated, leaving a yellow glass (V) (9·7 g.).

The material (IV) (3·5 g.) which was insoluble in water and chloroform contained magnesium. It was boiled for 2 hr. with hydrochloric acid (2N; 50 ml.), and the magnesium-free compound (2·75 g.; m. p. 204°), *ethyl 3 : 4-dihydro-6-nitro-4-oxocoumarin-3-carboxylate* (VI) was filtered off; it crystallised from chloroform as white needles, m. p. 205—206° (Found: C, 51·35; H, 3·35. $C_{12}H_9O_7N$ requires C, 51·6; H, 3·25%).

[26] Ropp, *J. Amer. Chem. Soc.*, 1950, **72**, 4459.
[27] Breslow, Baumgarten, and Hauser, *ibid.*, 1944, **66**, 1286.
[28] Hill, *Amer. Chem. J.*, 1900, **24**, 1.
[29] Simonsen and Rau, *J.*, 1917, **111**, 220.
[30] Clemo and Swan, *J.*, 1944, 274.
[31] Grimme and Schmitz, *Ber.*, 1951, **84**, 734.

2-Hydroxy-5-nitroacetophenone (VII).—(*a*) Ethyl 2-acetoxy-5-nitrobenzoylmalonate (V) (9·7 g.) was treated with water (19·5 ml.), sulphuric acid (9·7 ml.; *d* 1·84), and acetic acid (68 ml.), and the whole refluxed for 3—4 hr. White crystals separated soon after the addition of the acid but after 3 hr. little solid was present. Water (90 ml.) was then added and the mixture boiled for a further 2 hr. On cooling, the solution deposited the ketone (2·9 g.) as needles, m. p. 99—100°. To the filtrate was added water (50 ml.), and a further 0·2 g. of product gradually separated. Small amounts of material could be recovered by chloroform extraction of the mother-liquors.

The chroman (VI) (2·75 g.) was refluxed with sodium hydroxide solution (10%; 27 ml.) for 80 min., all dissolving. Acidification of the cooled solution caused the evolution of carbon dioxide and precipitation of the ketone (1·75 g.; m. p. 97—99°). Crystallisation from ethanol (20 ml.) gave pure material (1 g.; m. p. 99—100°), and concentration of the mother-liquors gave a further 0·3 g. of m. p. 99°. The combined yield of ketone (4·4 g.) represents 78% yield from the acid chloride.

When hydrolysis of ethyl 2-acetoxy-5-nitrobenzoylmalonate with more dilute acetic acid was attempted, a mixture of the chroman and ketone resulted.

(*b*) 2-Methoxy-5-nitroacetophenone (Mathieson and Newbery [32]) (0·2 g.) was dissolved in benzene (8 ml.), and aluminium chloride (0·2 g.) added (cf. Dilthey and Schumacher [33]). The mixture was refluxed for 8 hr., and then treated with water and a few drops of hydrochloric acid. The benzene layer was separated and the aqueous layer extracted with benzene. The benzene extracts were washed with dilute sodium hydroxide solution, which was then acidified and re-extracted with benzene. Evaporation of the dried (Na_2SO_4) solution yielded crystals (0·13 g.), m. p. 88—90°. Recrystallisation from aqueous ethanol gave material m. p. 95—98° (undepressed by the addition of material obtained by Allan and Loudon's method [34]).

Attempts to convert ethyl 2-methoxy-5-nitrobenzoylmalonate (Mathieson and Newbery [32]) directly into 2-hydroxy-5-nitroacetophenone by acid hydrolysis were unsuccessful.

The m. p. of 2-hydroxy-5-nitroacetophenone has been given as 98—99° (Allan and Loudon [34]), 99·5° (Joshi and Singh [35]), and 111—112° (Lindemann and Romanoff [36]). We found that material prepared by Allan and Loudon's method required to be crystallised several times before a melting point of 98—99° was attained.

4-Nitrocatechol.—2-Hydroxy-5-nitroacetophenone (4·4 g.) was dissolved in N-sodium hydroxide (24·5 ml.), and hydrogen peroxide (1·07 g., 1·3 mols.) in water (25 ml.) was added, in an atmosphere of nitrogen. The mixture was initially warmed to 40° and then N-sodium hydroxide (16·5 ml.) was added during 100 min. Soon after the beginning of the reaction starting material began to be precipitated, but the addition of extra alkali produced a very deeply coloured solution. The reaction mixture was kept overnight and, after the addition of more alkali (7 ml.) during 30 min., hydrochloric acid was added. Unchanged ketone (0·97 g.) was collected and washed with water and the combined filtrates were extracted with ether (70 ml.). The dried (Na_2SO_4) solution was evaporated, leaving 4-nitrocatechol, m. p. 168°. Recrystallisation from benzene–methanol gave yellow needles, m. p. 171—172°. By treating the recovered ketone with hydrogen peroxide a total yield of 3·5 g. of 4-nitrocatechol (93%) was obtained.

4-Nitroveratrole (VIII).—Crude 4-nitrocatechol (3·5 g.) in ether (40 ml.) was treated with a solution of diazomethane (3·15 g.) in ether (210 ml.), then kept at 0° for 2 days, and the solution was filtered and evaporated. The residue was taken up in benzene (60 ml.) and washed with dilute sodium hydroxide solution. The residue from the dried (Na_2SO_4) benzene was recrystallised from ethanol, giving 4-nitroveratrole (2·7 g.; m. p. 96—97°) and a further 0·3 g. (m. p. 94°) were obtained from the mother-liquors (73%).

4-Aminoveratrole.—4-Nitroveratrole (3 g.) in methanol (60 ml.) was hydrogenated at 50°/55 atm. in the presence of Raney nickel for 2 hr. The catalyst was filtered off and the methanol removed in a stream of nitrogen. The residue was distilled (b. p. 159°/14 mm.), giving the amine as a white solid, m. p. 88° (2·15 g., 86%).

3 : 4-*Dimethoxybenzaldehyde* (IX).—4-Aminoveratrole (2·2 g.), dissolved in a mixture of hydrochloric acid (3·3 ml.; *d* 1·18) and water (9 ml.), was diazotised by treatment with sodium nitrite (1·05 g.) in water (2 ml.). The solution was then made neutral to Congo-red by addition

[32] Mathieson and Newbery, *J.*, 1949, 1133.
[33] Dilthey and Schumacher, *Annalen*, 1936, **344**, 300.
[34] Allan and Loudon, *J.*, 1949, 821.
[35] Joshi and Singh, *J. Amer. Chem. Soc.*, 1954, **76**, 4993.
[36] Lindemann and Romanoff, *J. prakt. Chem.*, 1929, **122**, 214.

of crystalline sodium acetate (1·3 g.). A 10% solution of formaldoxime was prepared according to Beech's directions[10] and to this was added a solution of copper sulphate (0·4 g.), sodium sulphite (0·06 g.; anhyd.), and crystalline sodium acetate (10 g.) in water (12 ml.). The diazonium solution was introduced below the surface of the stirred formaldoxime solution at 10° during 20 min. The mixture was stirred at 10° for 1 hr. after which hydrochloric acid was added until the mixture was acid to Congo-red. Ferric alum (17·5 g.) was added and the whole refluxed for 1 hr. After cooling, the mixture was extracted with ether, the extract was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The residue was distilled, giving the aldehyde (1·2 g., 50%), b. p. 140—150° (bath)/2 mm.

2-p-*Methoxyphenylazo-2-nitroethanaldoxime*.—A neutral solution of *p*-methoxybenzenediazonium chloride (from *p*-anisidine, 3·1 g., 1 mol.) was run with stirring during 15 min. into a solution of methazonic acid (3·8 g., 1·5 mols.), copper sulphate (1·25 g.), sodium sulphite (0·1 g.; anhyd.), and hydrated sodium acetate (20 g.) in water (30 ml.) kept at 15°. A brown precipitate was produced, and after being kept overnight the mixture was acidified and filtered. The dry material (7·6 g.) was only partially soluble in ether; the ether-insoluble material contained copper but this was decomposed by shaking it with ether and dilute hydrochloric acid, giving material identical with that obtained from the initial extract. This *azo-compound* (5 g.) crystallised from ethanol as dark red prisms, m. p. 163° (Found: C, 45·5; H, 4·3; N, 23·4. $C_9H_{10}O_4N_4$ requires C, 45·4; H, 4·2; N, 23·5%).

Cyanomalondialdehyde.—A solution of sodium cyanomalondialdehyde was prepared by Uhle and Jacobs's method.[37] A mixture of cyanoacetaldehyde diethyl acetal (0·6 g.), ethyl formate (0·42 g.), and ether (2·5 ml.) was added to powdered sodium (0·1 g.). After 12 hr. at room temperature the sodium salt was extracted with water (1 ml.), and the solution was made just acid with dilute nitric acid. A concentrated aqueous solution of silver nitrate (0·75 g.) was added and the silver salt was quickly filtered and washed with a little water. The dry salt (0·5 g.) was suspended in ether, and dry hydrogen chloride was bubbled through it for 6 hr. The silver chloride was removed and the ether distilled, leaving the aldehyde (0·2 g.). This material gave, with aniline, an immediate precipitate, which when crystallised from ethanol had m. p. 129° (Uhle and Jacobs[37] give 132°).

o-Carboxy-N-3′-cyanopropylbenzamide.—When γ-phthalimidobutyronitrile was set aside in ethanolic sodium hydroxide it was converted into the *amide*, which separated from water as colourless crystals, m. p. 114° (Found: C, 62·0; H, 5·5; N, 11·95. $C_{12}H_{12}O_3N_2$ requires C, 62·05; H, 5·2; N, 12·05%). This compound was the major product obtained on the attempted formylation of γ-phthalimidobutyronitrile, in the presence of sodium ethoxide in ethanol. Attempts to bring about a condensation with ethyl formate under alcohol-free conditions were also futile.

6 : 7-*Dimethoxyisoquinoline* (XII).—This was prepared from 2-(3 : 4-dimethoxyphenyl)-ethylamine essentially as described by Späth and Polgar[12] except that the dehydrogenation was carried out as follows: 3 : 4-Dihydro-6 : 7-dimethoxy*iso*quinoline (0·36 g.) and palladium black (0·12 g.) were heated together in a bulb distillation apparatus at 180°/11 mm. After 30 min. more palladium (0·06 g.) was added and heating was continued for a further 30 min. The *iso*quinoline was then distilled from the palladium as an almost colourless liquid [0·33 g., b. p. 140—150° (bath)/0·1 mm.]. The product, in benzene, was boiled with charcoal and the residue from the filtered and evaporated solution was converted into the hydrochloride by the addition of concentrated hydrochloric acid. The crude, dry product was dissolved in a little ethanol; the hydrochloride (0·3 g.; m. p. 220°) separated on the addition of warm acetone. The regenerated base separated from benzene–light petroleum (b. p. 60—80°) as needles (0·2 g., 55%), m. p. 93°.

Cinchomeronic Acid (XIII).—6 : 7-Dimethoxy*iso*quinoline (172 mg.) was heated for 3 hr. with hydrochloric acid (2 ml.; *d* 1·18) at 160°. The whole was taken to dryness, nitric acid (2 ml.; *d* 1·42) added, and the mixture was then heated on the steam-bath for 12 hr. The nitric acid was evaporated and the crude cinchomeronic acid was crystallised from 0·5*N*-nitric acid (yield: 134 mg., 88%; m. p. 267°).

4-*Ethyl Hydrogen Cinchomeronate* (XIV).—This was prepared from the acid in 75% yield by Strache's method.[13] A neutral solution of the ammonium salt was prepared by treatment of the half ester (0·1 g.) with ammonia (1 mol.) in water (2 ml.); and the silver salt (0·14 g.) separated on the addition of a concentrated solution of silver nitrate (0·1 g.).

iso*Nicotinic Acid* (XVI).—The above silver salt was heated in a bulb distillation apparatus

[37] Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 76.

at atmospheric pressure. Decomposition occurred at about 180° and then the bath temperature was gradually raised to 300°. The distillate (XV) was refluxed with N-sodium hydroxide (1 ml.) for 30 min. and the solution was exactly neutralised with acetic acid. A concentrated solution of copper acetate (50 mg.) was added and after a few minutes the copper salt was filtered off, washed with water, and decomposed with hydrogen sulphide, the copper sulphide removed, and the filtrate evaporated, giving the acid (14 mg.), m. p. 310°.

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311. *The Lowest Singlet Excited Levels of Naphthalene. Part I. A Semi-empirical Calculation.**

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ASMO–CI (Antisymmetrical molecular orbital–configurational interaction) calculations have been carried out on naphthalene, with the approximations suggested by Pariser and Parr for evaluating the molecular integrals. The two lowest configurations in each of the symmetry classes $^1B_{1u}$ and $^1B_{2u}$ have been used, which make it possible, when using cyclic orbitals, to establish a relation with the functions built to resemble those of benzene. The lowest transition is found to be polarized along the long axis of the molecule ($^1B_{1u}$), and the second along the short axis ($^1B_{2u}$). The comparison of calculated f-values with the observed intensities is not entirely satisfactory, and some difficulties in the interpretation of the spectra are discussed.

PARISER and PARR [1] proposed a semi-empirical approximation by which the lowest excited levels of conjugated systems can be calculated with relative ease. Essentially three modifications are introduced into the non-empirical configuration interaction method of Coulson, Craig, and Jacobs [2] and others, which is derived from the classical treatment of benzene by Goeppert-Mayer and Sklar: [3] (1) the two-electron molecular integrals are approximated by linear combinations of only coulomb-type atomic integrals; (2) the values of these atomic integrals are changed from their analytically calculated values to empirical values; and (3) the monoelectronic core integrals between adjacent centres are also given empirical values.

Applied to *trans*-butadiene,[4] the procedure predicted with rather good accuracy the order, separations, and intensities of the N→V transitions. On the contrary, the results obtained by the non-empirical scheme are not so satisfactory.[5]

An investigation of naphthalene is a natural step towards the study of larger molecules of chemical and biological interest. In addition, there will be the opportunity to study the method of calculation for a molecule where the mechanism of electronic excitation is certainly not as simple as in a linear or a pseudo-linear system. In this paper this semi-empirical procedure will be used to investigate the lowest singlet–singlet transitions of napthalene. A later paper will be concerned with some restrictions that can be made on the present calculation to parallel treatments of the same problem recently proposed by Dewar and Longuet-Higgins [6] and by Moffitt.[7]

* A summary has been previously published (Moser and Lefebvre, *J. Chem. Phys.*, 1955, **23**, 598).

[1] Pariser and Parr, *J. Chem. Phys.*, 1953, **21**, 466, 767.
[2] Coulson, Craig, and Jacobs, *Proc. Roy. Soc.*, 1951, *A*, **206**, 297.
[3] Goeppert-Mayer and Sklar, *J. Chem. Phys.*, 1938, **6**, 645.
[4] Moser, *J.*, 1954, 3455.
[5] Lefebvre, Thesis, London, 1953; Pullman, *J. Chim. phys.*, 1954, **51**, 188.
[6] Dewar and Longuet-Higgins, *Proc. Phys. Soc.*, 1954, **67**, *A*, 795.
[7] Moffitt, *J. Chem. Phys.*, 1954, **22**, 320.

The calculation has been restricted to the two symmetry classes which correspond to allowed singlet π–π transitions from the ground state, and to the two lowest configurations within these classes. This choice has been made because: (1) There are reasons to believe that the lowest three singlet transitions of naphthalene are allowed even though the character of the first band has sometimes given rise to the interpretation of a forbidden transition.[8] But Platt [9] suggested that the weakness of the transition could be accounted for by a resemblance between naphthalene and a cyclic molecule. (2) The restriction to the lowest configurations of each of these symmetry classes makes it particularly easy to put the emphasis on this resemblance, since the use of cyclic molecular orbitals makes it possible to build from these configurations functions which would be convenient for the truly cyclic molecule. If there is any particular significance to be attached to this configurational interaction when using the cyclic orbitals, it would be also necessary to consider that same interaction when using other molecular orbitals not greatly different from these.

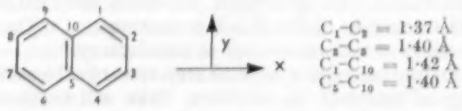
It was hoped that with this limited choice of configurations the qualitative nature of the various transitions would be characterized. Three parallel calculations have been carried out, with three different sets of orbitals: (*a*) the Hückel orbitals (cf. Coulson [10] for the definition of these orbitals); (*b*) the cyclic real orbitals, *i.e.*, the orbitals which result from the usual LCAO–MO (linear combination of atomic orbitals–molecular-orbital) theory applied to the molecule without its cross-bond (cf. Lefebvre [5] for the form of these orbitals); (*c*) the orbitals found from an investigation of the ground state by the SCF (self-consistent field) method.[11] These orbitals are those which are pertinent to the procedure adopted for the evaluation of the molecular integrals. These have been chosen because: (i) orbitals which are specific for the excited states are unknown; (ii) the cyclic orbitals have a particular meaning in relation with the "pseudo-cyclic" character of the molecule; (iii) the Hückel and the cyclic orbitals will be useful when comparing the results with those obtained in some recent investigations.

There will be a brief description of the calculations and in the Discussion section the results will be compared with the experimental observations on the ultraviolet spectrum of naphthalene, and the wave functions and levels proposed by Dewar and Longuet-Higgins [6] and Moffitt [7] for this molecule.

Calculations

The general procedure for the use of Pariser and Parr's method follows that of the usual configuration-interaction method, and so only a very brief outline of the calculations will be necessary here.

Naphthalene is assumed to have the following geometry: [12]



C_1–C_2 = 1·37 Å
C_2–C_3 = 1·40 Å
C_1–C_{10} = 1·42 Å
C_5–C_{10} = 1·40 Å

This numbering of the carbon atoms will be useful when using cyclic orbitals. The assumption of unequal bond lengths does not introduce unmanageable complications in the calculation.

From the ten $2p\pi$ atomic orbitals, ten independent real molecular orbitals can be obtained, $\phi_1 \ldots \phi_5$ being bonding, $\phi_6 \ldots \phi_{10}$ antibonding. From the results of the simple LCAO–MO theory [13] we infer that the two lowest singlet configurations of the class B_{2u} result from the monoexcitations $5 \longrightarrow 6$ and $4 \longrightarrow 7$, and the two lowest singlet configurations of the class B_{1u} from the monoexcitations $5 \longrightarrow 7$ and $4 \longrightarrow 6$. Functions belonging to B_{2u} transform as

[8] See, *e.g.*, Sponer and Nordheim, *Discuss. Faraday Soc.*, 1950, **9**, 19.
[9] Platt, *J. Chem. Phys.*, 1949, **17**, 484.
[10] Coulson, *Proc. Phys. Soc.*, 1948, **60**, *A*, 251.
[11] Moser, *J. Chim. phys.*, 1955, **52**, 24.
[12] Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 233; Ahmed and Cruickshank, *ibid.*, 1952, **5**, 852.
[13] Coulson, *Proc. Phys. Soc.*, 1948, **60**, *A*, 257.

does y and those belonging to B_{1u} as does x. The following wave function corresponds to the singlet excitation $i \longrightarrow j$:

$$^1\psi_1^{i,j} = (1/\sqrt{2})\left\{|\ldots\phi_i\bar{\phi}_j| - |\ldots\bar{\phi}_i\phi_j|\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

the orbitals not mentioned in the formula are all doubly occupied.

With the total Hamiltonian in the form used by Goeppert-Mayer and Sklar, the corresponding energy is : [14]

$$^1E_1^{i,j} = E_0 + \varepsilon_j - \varepsilon_i - J_{ij} + 2K_{ij} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where E_c is the ground-state energy and ε_k the quantity :

$$\int\phi_k^*[\mathrm{H}^c + \sum_{l=1}^{5}(2J_l - K_l)]\phi_k \mathrm{d}\tau = \varepsilon_k^c + \sum_{l=1}^{5}(2J_{kl} - K_{kl}) \quad . \quad . \quad . \quad . \quad (3)$$

In equation (3), H^c is the Hamiltonian of a π-electron in the absence of all other π-electrons. The energy expression (2) can then be reduced to a linear combination of two sorts of molecular integrals ;[15] the one-electron core integral :

$$\varepsilon_{kl}^c = \int\phi_k^*\mathrm{H}^c\phi_l \mathrm{d}\tau \text{ (with the notation } \varepsilon_k^c \text{ for } \varepsilon_{kk}^c) \quad . \quad . \quad . \quad . \quad (4)$$

and the two-electron repulsion integral :

$$\gamma_{pq}^{mn} = \int\phi_m(1)\,\phi_n(1)\,(e^2/r_{12})\phi_p(2)\,\phi_q(2)\,\mathrm{d}\tau_{12} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

of which the Coulomb and exchange molecular integrals J_{ij} and K_{ij} are special cases. For the off-diagonal matrix elements there is the formula :

$$\int {}^1\psi_k^{m,n*}\mathrm{H}^1\psi_1^{p,q}\mathrm{d}\tau = 2\gamma_{pq}^{mn} - \gamma_{nq}^{mp} \ (m \neq p,\ n \neq q) \quad . \quad . \quad . \quad . \quad (6)$$

The values of the atomic integrals are those used in the calculation of the SCF MO's.[11] The data for the molecular integrals are collected in Table 1. The calculated excitation energies, the calculated intensities (for which the calculated transition energies have been used), and the coefficients of the configurations in the wave-functions are collected in Table 2. C_{ke} is the coefficient which multiplies $^1\psi_1^{k,l}$ in a given wave-function.

A number of features of this calculation follow from the results given in Table 2. The order of levels before configurational interaction varies from one set to another, and is not as expected on the basis of the simple LCAO–MO method except when Hückel orbitals are used. The mixing of the configurations of the same symmetry class is considerable in all cases, and has the effect of reducing considerably the intensity of the two lowest transitions. As far as the two lowest levels are concerned, the final order is the same in all three calculations.

Discussion

It is generally accepted that there are in the near-ultraviolet spectrum three singlet–singlet transitions :[16] (1) 3·97 ev (f = 0·002), (2) 4·29 ev (f = 0·18), and (3) 5·6 ev (f = 1·70) These transitions have received various assignments. As mentioned above, the first band is generaliy regarded as representing an allowed transition, but there is disagreement as to whether this transition is polarized along the short (y) axis [17] or the long (x) axis of the molecule. Recent experimental work [18] indicates that the transition is polarized along the long axis of the molecule, and the second (also allowed) along the y axis.

From the point of view of symmetry assignments, the present results are in satisfactory agreement with McClure's recent assignments.[18] The first transition is $A_{1g} \longrightarrow B_{2u}$.

[14] Cf. Roothaan, *Rev. Mod. Phys.*, 1951, **23**, 69.
[15] Cf. Parr, Craig, and Ross, *J. Chem. Phys.*, 1950, **18**, 1561.
[16] Klevens and Platt, *ibid.*, 1949, **17**, 470.
[17] *E.g.*, Passerini and Ross, *ibid.*, 1954, **22**, 1012.
[18] McClure, *ibid.*, p. 1668.

TABLE 1.

Molecular integrals $\gamma_{ij} = \gamma_{ji}^{ij}$ $\delta_{ij} = \gamma_{ij}^{ij}$ (the molecular orbitals are real functions)

	Hückel	Cyclic	S.C.F.		Hückel	Cyclic	S.C.F.		Hückel	Cyclic	S.C.F.
γ_{11}	6·330	5·710	6·213	γ_{25}	5·787	5·842	5·688	δ_{17}	0·269	0·286	0·382
γ_{12}	5·452	5·472	5·491	γ_{26}	5·787	5·842	5·704	δ_{23}	0·338	0·255	0·421
γ_{13}	6·171	5·949	6·004	γ_{27}	5·706	6·054	5·976	δ_{24}	1·458	0·918	1·189
γ_{14}	5·910	5·804	6·128	γ_{44}	5·934	6·024	6·191	δ_{25}	0·757	0·757	0·819
γ_{15}	5·769	5·617	5·704	γ_{45}	5·502	5·584	5·594	δ_{26}	0·410	0·410	0·441
γ_{16}	5·769	5·617	5·718	γ_{46}	5·502	5·584	5·598	δ_{27}	0·381	0·387	0·229
γ_{17}	5·910	5·804	6·285	γ_{47}	5·934	6·024	6·319	δ_{34}	0·152	0·423	0·178
γ_{22}	5·544	5·544	5·526	γ_{55}	5·651	5·651	5·593	δ_{35}	1·186	0·919	1·314
γ_{23}	5·384	5·399	5·432	γ_{56}	5·651	5·651	5·604	δ_{36}	0·393	0·327	0·341
γ_{24}	5·601	5·551	5·569	γ_{57}	5·502	5·584	5·650	δ_{37}	0·358	0·465	0·513
γ_{25}	5·392	5·392	5·431	δ_{12}	0·979	1·562	1·107	δ_{45}	0·145	0·102	0·173
γ_{26}	5·392	5·392	5·428	δ_{13}	1·007	0·894	0·925	δ_{46}	0·556	0·781	0·400
γ_{27}	5·601	5·551	5·565	δ_{14}	0·633	0·621	0·731	δ_{47}	0·688	0·523	0·755
γ_{33}	6·111	6·498	5·907	δ_{15}	0·400	0·511	0·398	δ_{56}	0·798	0·798	0·681
γ_{34}	5·706	6·054	5·855	δ_{16}	0·232	0·274	0·214	δ_{57}	0·556	0·781	0·406
γ_{35}	−0·308	−0·233 *	0·314	δ_{17}^{26}	0·556	−0·781 *	0·402	δ_{67}^{25}	0·145	−0·102	0·142
$\varepsilon^0_1 - 10W_{2p}$	−55·8482	−53·5040	−55·6239	$\varepsilon^0_4 - 10W_{2p}$	−50·8585	−51·3943	−52·2178	$\varepsilon^0_6 - 10W_{2p}$	−45·4082	−45·4082	−45·2906
$\varepsilon^0_2 - 10W_{2p}$	−49·9516	−49·9516	−50·0890	$\varepsilon^0_5 - 10W_{2p}$	−49·2199	−49·2199	−49·0428	$\varepsilon^0_7 - 10W_{2p}$	−46·3869	−47·5374	−48·7543
$\varepsilon^0_3 - 10W_{2p}$	−52·6126	−53·6265	−52·0206								

* For the cyclic orbitals, ϕ_7 as defined analytically here, corresponds to minus the Hückel or SCF ϕ_7 orbital.

TABLE 2.

Transition energies (ev)			f values			Wave-functions
Hückel	Cyclic	S.C.F.	Hückel	Cyclic	S.C.F.	For all orbitals
			(a) *Before* C.I.			
$\Delta E_1^{5,6}$ (B_{2u}) 5·507	5·107	5·814	0·66	0·61	0·54	$C_{56} = 1$ $C_{47} = 0$
$\Delta E_1^{4,7}$ (B_{2u}) 5·984	4·525	5·719	0·52	0·23	0·47	$C_{56} = 0$ $C_{47} = 1$
$\Delta E_1^{5,7}$ (B_{1u}) 5·434	5·024	5·032	1·02	1·28	0·68	$C_{57} = 1$ $C_{46} = 0$
$\Delta E_1^{4,6}$ (B_{1u}) 5·889	5·594	5·996	1·11	1·42	0·78	$C_{57} = 0$ $C_{46} = 1$
			(b) *After* C.I.			Hückel / Cyclic / S.C.F.
4·668 (B_{1u})	3·819 (B_{1u})	4·696 (B_{1u})	0·02	0·02	0·13	$C_{57} = 0·784$ $C_{46} = -0·621$ / $C_{57} = 0·772$ $C_{46} = 0·636$ / $C_{57} = 0·892$ $C_{46} = -0·454$
4·984 (B_{2u})	4·180 (B_{2u})	4·995 (B_{2u})	0·05	0·00	0·00	$C_{56} = 0·806$ $C_{47} = 0·592$ / $C_{56} = 0·520$ $C_{47} = -0·853$ / $C_{56} = 0·685$ $C_{47} = 0·728$
6·542 (B_{2u})	5·939 (B_{2u})	6·333 (B_{1u})	1·28	1·01	1·51	$C_{56} = 0·592$ $C_{47} = -0·806$ / $C_{56} = 0·853$ $C_{47} = 0·520$ / $C_{57} = 0·454$ $C_{46} = -0·892$
6·655 (B_{1u})	6·799 (B_{1u})	6·538 (B_{2u})	2·47	3·43	1·15	$C_{57} = 0·621$ $C_{46} = 0·784$ / $C_{57} = 0·636$ $C_{46} = -0·772$ / $C_{56} = 0·728$ $C_{47} = 0·685$

The relative separations of levels is reasonably reproduced: 0·31 ev (Hückel), 0·36 ev (cyclic), 0·30 ev (SCF) compared with the 0·31 ev observed experimentally. Further, in all cases the first transition is very weak [respectively f = 0·02 (Hückel), 0·02 (cyclic), 0·13 (SCF) compared with the experimental value 0·002]. Keeping in mind the difficulty of obtaining precise f values, one should not expect better agreement from an approximate calculation.

From the point of view of relative intensities, the results are not as satisfactory, as the hundred-fold difference in observed f values between the first and the second band is not reproduced. In two of the three calculations (cyclic and SCF orbitals), the relative order is even reversed. In general, the intensities are more sensitive than the energies to the form of the wave-functions. But in view of the fact that in the present calculation the intensities of the two lowest transitions are in all cases very weak, regardless of the set of orbitals used, and that the two lowest levels are not widely separated, it might be possible that, if the calculation were improved, the order of the levels would be B_{2u} and then B_{1u}, again with very weak transition moments.

In other words, if we forget for a moment about the recent experimental symmetry assignment mentioned above, the calculations do not characterize satisfactorily the intensities and it is not possible to differentiate the two transitions, in contrast to the experimental spectrum.

This point will be discussed further, in relation with the semi-empirical procedures proposed by Dewar and Longuet-Higgins [6] and Moffitt.[7]

The Dewar and Longuet-Higgins Procedure.—The strict degeneracy which exists in the simple LCAO–MO theory between $^1E_1^{5,7}$ and $^1E_1^{4,6}$ causes an equal mixing of $^1\psi_1^{5,7}$ and $^1\psi_1^{4,6}$. The two other functions $^1\psi_1^{5,6}$ and $^1\psi_1^{4,7}$ are assumed not to mix. From the sign of the off-diagonal matrix element:

$$\int {}^1\psi_1^{5,7*}\, H\, {}^1\psi_1^{4,6}\, d\tau \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

it results that the function:

$$2^{-\frac{1}{2}}[{}^1\psi_1^{5,7} - {}^1\psi_1^{4,6}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

is the lower. This produces zero transition moment. In this method the two lowest transitions (the other one being the monoexcitation $5 \longrightarrow 6$) are well differentiated by their intensities. The exact order of levels is not calculated but one makes a one-to-one correspondence with the experimental transitions, taking advantage of the fact that they are also well characterized by their transition moments.

As mentioned above, when the calculations are made with the Hückel orbitals, an order of levels that follows that of the simple theory is obtained before configuration interaction. $^1E_1^{5,7}$ and $^1E_1^{4,6}$ are close together. In consequence there is a nearly equal mixing of the functions $^1\psi_1^{5,7}$ and $^1\psi_1^{4,6}$ and, as a result, there is nearly a vanishing transition moment, which is characteristic of Dewar and Longuet-Higgins's procedure. However here it is found that the mixing of $^1\psi_1^{5,6}$ and $^1\psi_1^{4,7}$ is considerably more than that assumed in the above procedure. A large decrease in the f value follows (0·05 instead of 0·66 for the pure $5 \longrightarrow 6$ excitation). This is due, in part, to the fact that the levels are rather close to each other.

In the other cases (cyclic and SCF orbitals), the mixing is important in both classes, and in one instance (SCF orbitals) is even more important for the B_{2u} class than for the B_{1u} class. Obviously, in the *a priori* calculation presented here, there is no clear-cut distinction between the two classes, in contrast to the Dewar and Longuet-Higgins scheme.

The effect of mixing of the two configurations in each of the two symmetry classes for both Hückel and cyclic orbitals is presented in Figs. 1 and 2. An arbitrary excitation energy of 30·000 cm.$^{-1}$ has been used in the calculation of these graphs. Two points may be specifically mentioned: (1) Even a small amount of mixing for the class $^1B_{1u}$ has the effect of reducing considerably the intensity calculated from a single configuration. (2) Accidentally, one might calculate zero intensity for either class or perhaps even for both classes.

Moffitt's Procedure.—The cyclic real orbitals used above can be deduced, by the use of symmetry conditions, from the cyclic complex orbitals which have the form :

$$\phi_l = 10^{-\frac{1}{2}} \sum_k \exp\,[2\pi ikl/10]\ \chi_k \quad (l = 0, \pm 1, \ldots \pm 4, 5)$$

In the ground state, the orbitals up to $l \pm 2$ are doubly occupied. From the four lowest singlet monoexcited wave-functions :

$$^1\psi_1^{-2,-3},\ ^1\psi_1^{2,3},\ ^1\psi_1^{-2,3},\ ^1\psi_1^{2,-3}$$

Moffitt forms the following combinations :

$$\left.\begin{array}{ll} \Theta_X = (1/\sqrt{2})\ (^1\psi_1^{-2,-3} + {}^1\psi_1^{2,3}) & \Theta_U = (1/\sqrt{2})\ (^1\psi_1^{-2,3} + {}^1\psi_1^{2,-3}) \\ \Theta_Y = (1/i\sqrt{2})\ (^1\psi_1^{-2,-3} - {}^1\psi_1^{2,3}) & \Theta_V = (1/i\sqrt{2})\ (^1\psi_1^{-2,3} - {}^1\psi_1^{2,-3}) \end{array}\right\} \quad . \quad (9)$$

which satisfy the symmetry requirements for naphthalene, and also correspond to the lowest singlet functions of the truly cyclic molecule. The notation is the same as that used

FIG. 1.

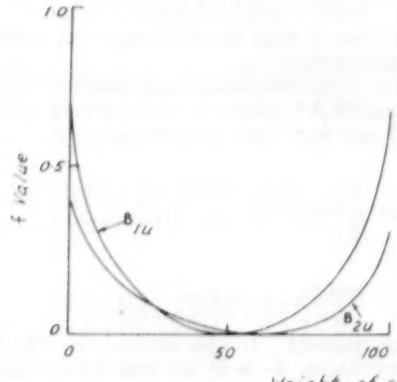
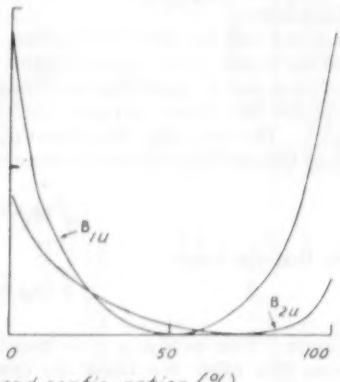


FIG. 2.



Weight of second configuration (%)

The effect of mixing of configurations on the f *value* : FIG. 1, *Hückel orbitals*; FIG. 2, *cyclic orbitals*

by Moffitt. After allowance for the mixing of the functions belonging to the same symmetry class, the final functions are, in order of increasing energy :

$$\Theta_V,\ \cos\rho\ \Theta_U + \sin\rho\ \Theta_X,\ \Theta_Y,\ \cos\rho\ \Theta_X - \sin\rho\ \Theta_U$$

A comparison with the wave-functions in Table 2, built from real cyclic orbitals, is possible because of the following identities, which result from the relations between complex and real cyclic orbitals :[5]

$$\left.\begin{array}{ll} ^1\psi_1^{5,6} = (1/\sqrt{2})\ (\Theta_X - \Theta_U) & ^1\psi_1^{4,6} = (1/\sqrt{2})\ (\Theta_V - \Theta_Y) \\ ^1\psi_1^{5,7} = (1/\sqrt{2})\ (\Theta_V + \Theta_Y) & ^1\psi_1^{4,7} = (1/\sqrt{2})\ (\Theta_X + \Theta_U) \end{array}\right\} \quad . \quad . \quad (10)$$

Thus the lowest excited wave-function, that is, Θ_V, is seen to result in Moffitt's procedure when equal weights are given to the functions $^1\psi_1^{5,7}$ and $^1\psi_1^{4,6}$. In the present calculation the lowest level corresponds to the wave-function :

$$0{\cdot}636\ ^1\psi_1^{4,6} + 0{\cdot}772\ ^1\psi_1^{5,7}$$

which does not depart notably from equal mixing. From the identities (10), one sees that the large mixing which exists in Table 2, between the singlet monoexcited wave-functions built on real cyclic orbitals, has as a counterpart a small mixing of the functions built to

resemble those of a truly cyclic molecule. The present calculation agrees qualitatively with that of Moffitt, in the sense that in both cases emphasis is put on the functions (9) rather on the functions ${}^1\psi_1^{5,7}$. However it must be noticed that the mixing between Θ_U and Θ_X is somewhat larger in Moffitt's procedure than that resulting from the data of Table 2. Another circumstance is worth mentioning: in both empirical procedures (Dewar and Longuet-Higgins's and Moffitt's) the lowest level is described by an equal mixing of ${}^1\psi_1^{5,7}$ and ${}^1\psi_1^{4,6}$ although the orbitals are not the same. This will be the object of detailed analysis in a later paper.

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312. *Nucleophilic Displacement Reactions in Aromatic Systems. Part V.* Kinetics of the Reactions of Some Chloroazanaphthalenes and Related Compounds with Ethoxide Ions and with Piperidine.*

By N. B. Chapman and D. Q. Russell-Hill.

Heats and entropies of activation for the reactions in ethanol of ethoxide ion and of piperidine with a series of chloro-heterocyclic compounds (1- and 2-chloro-mono- and -di-azanaphthalenes and chloro-mono- and -di-azabenzenes) and with 5-chloroacridine and *o*-chloronitrobenzene have been determined. The results provide experimental evidence about the validity of a simplified quantum-mechanical theory of aromatic nucleophilic substitution due to Longuet-Higgins.[1] It is concluded that, while the theory leads to qualitatively correct results, it is only valid in a semiquantitative way, even over a restricted range of compounds.

There is no evidence at present of cine-substitution, or of an elimination-addition mechanism in these reactions, but additional evidence of acid-catalysis in this class of reactions is presented.

Variations of reactivity caused by the fusion of a benzene ring to 2- or 4-chloropyridine in various possible ways, and to 2-chloropyrimidine, are discussed, especially with respect to bond-fixation in the 2 : 3-position in naphthalene and similar compounds.

Our previous studies in this field have been confined to monocyclic compounds. We now turn to dicyclic compounds, with the special object of providing quantitative experimental results for comparison with a simplified quantum-mechanical theory of nucleophilic aromatic substitution due to Longuet-Higgins.[1] This theory, although apparently unsuccessful even qualitatively when applied to the reactions of azabenzene derivatives, cf. Tables 3 and 4, is much more successful qualitatively when applied to reactions of mono- and di-azanaphthalene derivatives. The present paper records chiefly studies of the reactions of 1- or 2-chloro-mono- and -di-azanaphthalenes, including quinoline, *iso*-quinoline, quinazoline, cinnoline, phthalazine, and quinoxaline derivatives. The reactions of some analogous monocyclic compounds and of 2-chloronaphthalene and 5-chloro-acridine are included for comparison. Preliminary accounts of this work have already been given.[2] Some closely related reactions have been studied by Young and Amstutz,[3] and by Brower, Samuels, Way, and Amstutz,[4] and are discussed below (p. 1570).

* Part IV, *J.*, 1954, 2109.

[1] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265; *Nature*, 1950, **166**, 139; cf. Dewar, "Progress in Organic Chemistry," Butterworths, London, 1953, Vol. II, p. 1.

[2] (*a*) Chapman and Russell-Hill, *Chem. and Ind.*, 1954, 281, 1298; (*b*) Chapman, *Chem. Soc. Spec. Publ.*, No. 3, 1955, p. 155.

[3] Young and Amstutz, *J. Amer. Chem. Soc.*, 1951, **73**, 4773.

[4] Brower, Samuels, Way, and Amstutz, *J. Org. Chem.*, 1953, **18**, (*a*) 1075, (*b*) **1684**; 1954, **19**, (*c*) **411**, (*d*) 1830.

Experimental

Unless otherwise stated light petroleum (b. p. 40—60°) which had been dried over sodium, was used for crystallisation.

Materials.—Chloro-compounds. 2-Chloroquinoline (from British Drug Houses Ltd.) was recrystallised and had m. p. 37—38°. 4-Chloroquinoline was prepared by the method of Riegel and his co-workers,[5] and after recrystallisation had m. p. 30°. 1-Chloro*iso*quinoline was prepared by Fisher and Hamer's method [6] and freed from 1 : 4-dichloro*iso*quinoline by dissolution in hydrochloric acid, removal of the undissolved dichloro-compound, and recovery of the 1-chloro*iso*quinoline as usual. After recrystallisation it had m. p. 36—37°. 3-Chloro-*iso*quinoline, m. p. 46—48° after recrystallisation, was prepared by reduction of 1 : 3-dichloro-*iso*quinoline,[7] itself prepared by Gabriel's method [8] starting from homophthalimide.[9] 5-Chloroacridine was prepared by the method given by Albert [10] and purified by recrystallisation from slightly ammoniacal ethanol, and had m. p. 119·5—120·5°. 4-Chloroquinazoline, m. p. 98—100°, was prepared by Chapman, Gibson and Mann's method,[11] and 2-chloroquinazoline by Gabriel's method [12] to m. p. 107·5—108°. 4-Chlorocinnoline, m. p. 75—76° after crystallisation from light petroleum (b. p. 80—100°), was prepared by Leonard and Boyd's method,[13] and 1-chlorophthalazine by Gabriel's method [14]; this had m. p. 113° after crystallisation from dry ether. 2-Chloroquinoxaline (from Merck and Co., Inc.) was recrystallised and had m. p. 46·5—47°. 2-Chloropyridine (from L. Light & Co.) was purified from neutral impurities as usual and fractionated, a fraction of b. p. 168—170°/760 mm., n_D^{25} 1·5300, being collected; Rogers and Campbell [15] give n_D^{25} 1·5304. 4-Chloropyridine, which was stored at −78°, was prepared by Wibaut and Broeckman's method [16] by use of 4-hydroxypyridine [17] and had n_D^{20} 1·5313; Leis and Curran [18] give n_D^{20} 1·5315. 2-Chloropyrimidine and *o*-chloronitrobenzene were prepared as described in Parts III [19] and IV [19] respectively. 2-Chloronaphthalene prepared by a Sandmeyer reaction from 2-naphthylamine was recrystallised from aqueous ethanol and had m. p. 57°.

Amines, sodium ethoxide, and solvent. Piperidine and morpholine were purified as described in Part III.[19] Sodium ethoxide solutions were prepared by dissolving clean sodium in 99·8% ethanol, prepared as described in Part I,[20] and standardised acidimetrically. The carbonate content was also determined and this was usually negligible. 99·8% Ethanol was used as solvent throughout this investigation, unless otherwise stated (p. 1566).

Reaction Products.—These were isolated where necessary from solutions used in kinetic experiments or prepared independently under conditions very similar to those used in kinetic experiments. Selected known reaction products were characterised by their m. p.s. Most of the reactions studied had been shown by previous investigators to yield the expected products, *e.g.*, with hot ethanolic sodium ethoxide 2-chloroquinoline yields 2-ethoxyquinoline,[21] and 1-chlorophthalazine yields 1-ethoxyphthalazine.[22] 4-Chloroquinoline with hot methanolic sodium methoxide yields 4-methoxyquinoline,[23] and it is safe to assume a similar reaction with sodium ethoxide.

Procedure.—For reactions with amines in the range 20—40° this was as described in Part III,[19] save that for the reactions of 4-chloroquinazoline the procedure of Part I [20] was adopted. The essential feature was a Volhard determination of chloride ion. For reactions with amines in the range 50—160°, and for all ethoxide reactions, the method of sealed bulbs was used. All

[5] Riegel, Lappin, Adelson, Jackson, Albisetti, jun., Dodson, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1264.
[6] Fisher and Hamer, *J.*, 1933, 1904.
[7] Haworth and Robinson, *J.*, 1948, 777.
[8] Gabriel, *Ber.*, 1886, **19**, 1653.
[9] Harriman, Shelton, Van Campen, and Warren, *J. Amer. Chem. Soc.*, 1945, **67**, 1481.
[10] Albert, "The Acridines," Edward Arnold & Co., London, 1951, p. 152.
[11] Chapman, Gibson, and Mann, *J.*, 1947, 890.
[12] Gabriel, *Ber.*, 1896, **29**, 1313.
[13] Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 409.
[14] Gabriel, *Ber.*, 1893, **26**, 523.
[15] Rogers and Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 1209.
[16] Wibaut and Broekman, *Rec. Trav. chim.*, 1939, **58**, 885.
[17] König and Greiner, *Ber.*, 1931, **64**, 1052.
[18] Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79.
[19] Chapman and Rees, *J.*, 1954, 1190; Chapman, Parker, and Soanes, *J.*, 1954, 2109.
[20] Bishop, Cavell, and Chapman, *J.*, 1952, 437.
[21] Friedländer and Ostermaier, *Ber.*, 1882, **15**, 332.
[22] Von Rothenburg, *J. prakt. Chem.*, 1895, **51**, 149.
[23] Meyer, *Monatsh.*, 1906, **27**, 255, 987.

experiments were carried out in duplicate and independently determined mean values of k rarely differed by more than 1%. In certain cases the rate coefficients thus obtained were checked by determination of the consumption of ethoxide ion, by pouring reaction mixtures into an excess of standard hydrochloric acid and back-titration with standard sodium hydroxide.

Results

Detailed values for some of the reactions studied are given in Table 1 and all the results are summarised in Table 2. Evidence of order of reaction is provided for the reaction of 2-chloroquinoline with ethoxide ions, and the internal consistency of the rate coefficients together with

Table 1.

Reactions of piperidine.

1-*Chloroisoquinoline at* 110·0°. a = 0·4032M, b = 0·1037M.

Time (hr.)	1·00	2·25	4·00	6·05	8·00	12·00	16·00	20·00
Decompn. (%)	10·2	20·8	33·0	44·3	52·4	64·9	73·7	80·3
10^3k	8·52	8·50	8·48	8·57	8·46	8·48	8·52	8·61

Mean k = 8·52 ± 0·04 × 10^{-3}

2-*Chloroquinazoline at* 20·0°. a = 0·1928M, b = 0·0514M.

Time (min.)	30·0	55·0	80·0	110·0	150·0	215·0	250·0	310·0
Decompn. (%)	15·0	24·7	33·3	41·2	50·0	61·7	65·8	72·4
10^4k	4·86	4·79	4·85	4·78	4·73	4·82	4·74	4·77

Mean k = 4·79 ± 0·04 × 10^{-4}

Reactions of ethoxide ions.

2-*Chloroquinoline at* 80·0°. a = 0·2470M, b = 0·1013M.

Time (min.)	21·5	40·5	80·0	102·0	130·0	170·0	220·0	255·0
Decompn. (%)	13·3	23·0	39·1	45·7	53·6	61·9	71·0	75·1
10^4k	4·96	4·92	4·94	4·86	4·90	4·86	4·96	4·94

Mean k = 4·92 ± 0·03 × 10^{-4}. Order with respect to ethoxide ion 1·0; with respect to 2-chloroquinoline 0·97 (by differential method).

Mean k = 4·86 ± 0·03 × 10^{-4}, determined by ethoxide consumed (a = 0·2260, b, 0·1041M).

4-*Chloroquinoline at* 80·0°. a = 0·2550M, b = 0·1021M.

Time (min.)	30·0	60·0	105	150	210	295	335	480	∞
Decompn. (%)	10·4	19·6	30·5	40·3	49·8	60·8	65·5	76·7	99·7
10^4k	2·60	2·66	2·60	2·64	2·60	2·60	2·64	2·66	—

Mean k = 2·62 ± 0·02 × 10^{-4}

3-*Chloroisoquinoline* at 130·0°. a = 0·1084M, b = 0·0545M.

Time (hr.)	9·75	18·0	21·25	30·0	45·0	60·0	75·0	90·0
Decompn. (%)	13·6	23·5	26·8	34·9	46·1	54·7	61·5	67·5
10^3k	(4·63)	4·74	4·72	4·72	4·72	4·70	4·67	4·76

Mean k = 4·72 ± 0·02 × 10^{-3}

1-*Chlorophthalazine at* 30·0°. a = 0·1256M, b = 0·0522M.

Time (min.)	4·0	8·0	11·0	16·0	21·0	27·5	35·0	42·0	∞
Decompn. (%)	13·0	23·6	30·6	40·2	48·5	56·9	64·4	70·9	99·8
10^3k	4·80	4·75	4·78	4·76	4·78	4·77	4·73	4·83	—

Mean k = 4·77 ± 0·02 × 10^{-2}

previous experience in this field is taken as sufficient evidence of second-order reactions for the remaining examples. Rate coefficients are given as l. mole^{-1} sec.$^{-1}$. Errors in k given after the ± sign are mean deviations from the mean. Temperatures in the range 20—110° are accurate to ±0·04° or better, and in the range 120—160° to about ±0·2°. For the reactions of amines the second-order rate coefficient, k, is given by

$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10}\left(\frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}\right)$$

and for ethoxide ion reactions by

$$k = \frac{1}{t(a - b)} 2{\cdot}303 \log_{10}\left(\frac{b}{a} \cdot \frac{a - x}{b - x}\right)$$

TABLE 2. *Values of* 10^5k.

Reagent:	Ethoxide ion			Piperidine		
Temp.:	20·0°	30·0°	40·0°	20·0°	30·0°	40·0°
Chloro-compound	(i)	(i)	(i)	(i)	(i)	(i)
2-Chloroquinazoline	296—305	782—790	1840—1910	47·3—48·6	87·3—90·1	160—165
2-Chloroquinoxaline	821—854	1930	114—118 †	6·29—6·43	12·0—12·2	—
1-Chlorophthalazine	182—190	473—483	1080—1150	14·1—14·6 *	25·1—25·5 *	41·3—42·6 *
4-Chlorocinnoline	474—490	1140—1180	154—163 ‡	—	—	—
5-Chloroacridine	94·0—96·6 *	15·6—16·1	39·6—40·8	—	—	—
2-Chloropyrimidine	159—165	413—436	1030—1060	—	—	—
	70·0°	80·0°	90·0°	90·0°	100·0°	110·0°
2-Chloroquinoline	18·7—19·2	48·6—49·6	121—123	2·59—2·66	4·72—4·87	7·90—8·33
1-Chloroisoquinoline	19·2—19·7	49·8—51·0	7·34—7·54 §	2·95—3·04	4·94—5·12	8·46—8·61
4-Chloroquinoline	11·2—11·4	26·0—26·6	57·4—59·0	—	—	—
4-Chloropyridine	15·8—16·4 *	33·2—33·8 *	7·26—7·37	—	—	—
o-Chloronitrobenzene	115—118 *	18·9—19·5	48·5—49·9	—	—	—
	120·0°	130·0°	140·0°	130·0°	145·0°	160·0°
2-Chloropyridine ¶	23·0—23·6	54·2—55·6	123—126	0·569—0·597	1·41—1·50	3·18—3·36
3-Chloroisoquinoline	1·62—1·69	4·67—4·76	13·5—14·1	—	0·111—0·117 ‖	—

(i) Extreme values of 10^5k in l. mole^{-1} sec.$^{-1}$ for a given experiment. Values of k are usually accurate to ± 2%. Not less than 70% of the reaction was usually studied (for mean k's at 20·0° see Tables 3 and 4).

* 30° higher. † At 0·0°. ‡ At 8·85°. § At 60·0°. ‖ At 150·0°.

¶ For this compound $k_2 = 1{\cdot}00 \times 10^{-4}$ at 110·6°, and $1{\cdot}40 \times 10^{-5}$ at 90·0°, for reactions with ethoxide ion.

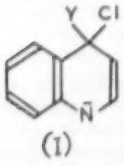
The values for the reaction of 2-chloroquinoxaline with ethoxide ion were determined by Mr. A. G. McKenna, whom we thank for unpublished results. They refer to anhydrous ethanol as solvent, but this change is only of minor importance, and is disregarded at present.

where a is the initial amine or ethoxide-ion concentration and b the initial concentration of chloro-compound. Analytically determined mean values of k were checked against values obtained by plotting t against $\log_{10}(0{\cdot}5a - x)/(b - x)$ or $\log_{10}(a - x)/(b - x)$. For all runs above 40° a correction for the expansion of ethanol was introduced into the calculation of the rate coefficients. Chloride determinations at "infinite" time (at least 30 times the half-life of the reaction) gave values of 99·7—100·1% reaction, thus confirming the purity of the chloro-compounds and indicating the absence of significant reversibility.

The courses of the reactions of 4-chloroquinoline with piperidine, and of 4-chloroquinazoline with pyridine, are displayed in Figs. 1 and 2. Analogous phenomena were observed in the reactions of morpholine with 2-chloropyridine at 160° and 2-chloroquinoline at 90° (Fig. 1, *B*); and of 4-chloropyridine at 100° and 5-chloroacridine at 40° with piperidine.

DISCUSSION

As in previous communications in this series, we assume a one-stage bimolecular mechanism for the reactions studied, since they show the kinetic, structural, and environmental properties characteristic of such a mechanism. Moreover, we have no evidence of the intervention of stable intermediates of type (I), although we have always regarded this type of structure as "providing a good guide to the nature of the transition state," as Hammond [24] recently emphasised. Furthermore, we have no evidence of "cine-substitution" [25] or of the intervention of the elimination-addition mechanism discovered by J. D. Roberts and his co-workers,[26] an example of which in the heterocyclic series has recently been brought to light in the reaction of 3-bromopyridine with sodioacetophenone.[27] The last two phenomena are most likely to be observed in the least activated substitutions, *e.g.*, reactions **1**, **6**, and **7**, Table 3. We have isolated 2-ethoxynaphthalene from the reaction of 2-chloronaphthalene and assume that 3-chloro*iso*quinoline gives the 3-ethoxy-compound since this reaction is a more activated substitution



(I)

[24] Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[25] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 382.
[26] J. D. Roberts and co-workers, *J. Amer. Chem. Soc.*, 1953, **75**, 3290.
[27] Levine and Leeke, *Science*, 1955, **121**, 780.

than that of 2-chloronaphthalene. We hope to verify this point experimentally in due course. Cine-substitution and the elimination-addition mechanism are both to be disregarded for reactions **3**, **4**, **9**, **13**, and **14** on structural grounds. Even high-temperature solvolysis of halogenoquinolines by piperidine has been shown [4b] not to involve cine-substitution, so that it is clearly justifiable to disregard this for the reactions of piperidine in dilute solution listed in Table 4. We have also shown previously [19] that ion exchange between piperidine and ethanol is unlikely to be significant in this class of reaction.

We interpret the results displayed in Figs. 1 and 2 as providing further evidence in favour of acid catalysis of nucleophilic displacements from basic heterocyclic systems (cf. ref. 19). It is noteworthy that the reaction of 4-chloroquinoline with piperidine in dilute solution shows rising rate coefficients as the reaction proceeds, as will be clear from Fig. 1, but steady coefficients in solvolysis with piperidine,[4b] whereas 2-chloroquinoline

FIG. 1. *A, Reaction of* **4**-*chloroquinoline* (0·1M) *with piperidine* (0·4M) *at* 90°.
B, Reaction of 2-*chloroquinoline* (0·1M) *with morpholine* (0·4M) *at* 90°.

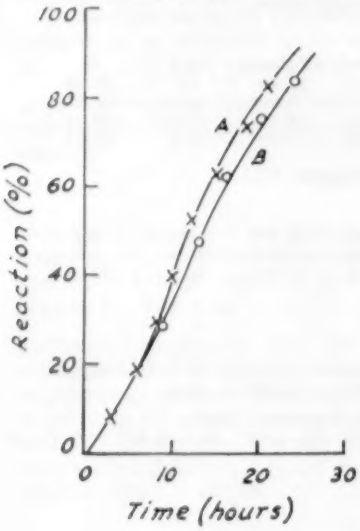
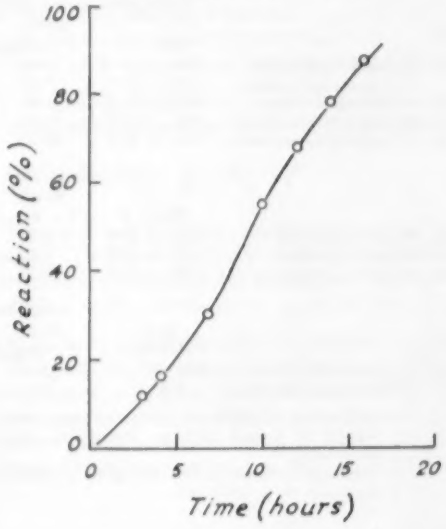


FIG. 2. *Reaction of* 4-*chloroquinazoline* (0·05M) *with pyridine* (0·20M) *at* 40°.



shows regular second-order kinetics in dilute solution. We relate this to a significant difference in basic strength between 2- and 4-chloroquinoline, a view confirmed by recent independent spectroscopic measurements giving for 4-chloroquinoline $K_b = 2{\cdot}6 \times 10^{-11}$. It was, however, found that "2-chloroquinoline is such a weak base that a constant could not be determined." [28] This is to be understood on the basis of a much stronger $-I$ effect of chlorine, which is more base-weakening, in the 2-position than in the 4-position, offset by base-strengthening mesomeric effects. However, with a reagent more weakly basic than piperidine (pK_b 2·8), *viz.*, morpholine (pK_b 5·6), 2-chloroquinoline seems to be able to compete successfully for protons, as indicated by the rising rate coefficients implied in curve *B*, Fig. 1. The situation as to basic strength and resultant reactivity is almost certainly the same for 2- and 4-chloropyridine. Thus 2-chloropyridine shows regular kinetics with piperidine but not with morpholine, whereas 4-chloropyridine shows rising coefficients even with piperidine. The suggestion of Brower *et al.*[4b] that the predominating reaction here is the polymerisation of 4-chloropyridine seems to us unlikely in view of the relative "nucleophilic powers" of piperidine and pyridine. Similar phenomena are also

[28] Knight, Wallick, and Balch, *J. Amer. Chem. Soc.*, 1955, **77**, 2577.

displayed in Fig. 2, but the reactions here are further complicated by a significant ethanolysis of 4-chloroquinazoline. The formation of acid in the reaction of pyridine with 4-chloroquinazoline is ascribed, as in a similar case in Part III,[19] to solvolysis of a first formed quaternary salt, with liberation of protons. Brower *et al.*,[45] however, obtained satisfactory second-order coefficients for the reaction of 4-chloroquinazoline with piperidine at low temperatures. In toluene solution, in which piperidine hydrochloride is very

TABLE 3.* *Reactions of ethoxide ions.*

Compound	20·0°, 10^5k	20·0°, $7 + \log_{10} k$	E (cal. mole^{-1})	$\Delta H^\ddagger$ (cal. mole^{-1})	$-\Delta S^\ddagger$ (cal. mole^{-1} deg.$^{-1}$)	$\Delta U - \Delta U^0$ (cal. mole^{-1} deg.$^{-1}$)
1-Chloro-mono- and -di-azanaphthalenes.						
1. 1-Chloronaphthalene †	—	—	—	—	—	0
2. 4-Chloroquinoline	0·065	0·81	20,400	19,700	19·6	12$\frac{3}{3}$3
3. 1-Chloro*iso*quinoline ...	0·069	0·84	22,500	21,800	12·3	12$\frac{3}{3}$3
4. 1-Chlorophthalazine ...	186	4·27	16,500	15,900	16·9	20$\frac{3}{3}$3
5. 4-Chlorocinnoline	477	4·68	15,800	15,200	17·3	20$\frac{3}{3}$3
2-Chloro-mono- and -di-azanaphthalenes.						
	20·0°, k	20·0°, $17 + \log_{10} k$				
6. 2-Chloronaphthalene...	$9{\cdot}1 \times 10^{-17}$	0·96	~39,000 §	~38,000 §	2·0	0
7. 3-Chloro*iso*quinoline ...	$1{\cdot}2 \times 10^{-11}$	6·07	32,400	31,600	0·7	3$\frac{3}{2}$4
8. 2-Chloroquinoline	$6{\cdot}3 \times 10^{-7}$	10·80	23,100	22,400	10·7	12$\frac{3}{2}$4
9. 2-Chloroquinazoline ...	$2{\cdot}98 \times 10^{-5}$	14·47	16,800	16,200	15·9	15$\frac{3}{2}$4
10. 2-Chloroquinoxaline ...	$8{\cdot}28 \times 10^{-5}$	14·92	15,400	14,800	18·2	15$\frac{5}{2}$4
Chloro-mono- and -di-azabenzenes.						
	20·0°, k	20·0°, $9 + \log_{10} k$				
11. 2-Chloropyridine	$2{\cdot}2 \times 10^{-3}$	0·34	26,800	26,200	9·2	$\frac{3}{3}$
12. 4-Chloropyridine	$8{\cdot}7 \times 10^{-3}$	1·94	20,900	20,200	22·3	$\frac{3}{3}$
13. 2-Chloropyrimidine ...	$1{\cdot}63 \times 10^{-2}$	6·21	16,900	16,300	15·7	2$\frac{3}{3}$
Miscellaneous.						
	20·0°, 10^7k	20·0°, $7 + \log_{10} k$				
14. 5-Chloroacridine	620	2·79	17,600	17,000	20·0	4$\frac{3}{1}$0
15. *o*-Chloronitrobenzene	1·8	0·25	23,700	23,000	10·8	—

* Values calculated from Arrhenius parameters given to 2 significant figures. Values of E and $\Delta H^\ddagger$ are usually accurate to ± 300 cal. mole^{-1}, and of $\Delta S^\ddagger$ to ± 1·1 cal. mole^{-1} deg.$^{-1}$.

† Preliminary experiments indicated irregular kinetics.

§ Accurate to ± 1000 cal.

TABLE 4.* *Reactions of piperidine.*

Compound	20·0°, k	20·0°, $7 + \log_{10} k$	E (cal. mole^{-1})	$\Delta H^\ddagger$ (cal. mole^{-1})	$-\Delta S^\ddagger$ (cal. mole^{-1} deg.$^{-1}$)	$\Delta U - \Delta U^0$ (cal. mole^{-1} deg.$^{-1}$)
1-Chloro-mono- and -di-azanaphthalenes.						
1. 1-Chloro*iso*quinoline ...	$2{\cdot}5 \times 10^{-7}$	0·40	14,500	13,800	41·9	12$\frac{3}{3}$3
2. 1-Chlorophthalazine ...	$2{\cdot}0 \times 10^{-6}$	2·31	11,800	11,100	42·0	20$\frac{3}{3}$3
3. 4-Chloroquinazoline †...	3·1	7·49	7,000	6,600	37·5	24$\frac{3}{3}$3
2-Chloro-mono- and -di-azanaphthalenes.						
4. 2-Chloroquinoline	$1{\cdot}5 \times 10^{-7}$	0·18	15,600	14,900	38·9	12$\frac{3}{2}$4
5. 2-Chloroquinoxaline ...	$6{\cdot}36 \times 10^{-6}$	2·79	11,300	10,800	40·9	14$\frac{3}{2}$4
6. 2-Chloroquinazoline ...	$4{\cdot}79 \times 10^{-4}$	3·68	11,100	10,500	37·8	15$\frac{3}{2}$4
Chloroazabenzenes.						
7. 2-Chloropyridine	$4{\cdot}8 \times 10^{-10}$	−2·32	19,900	19,100	35·8	$\frac{3}{3}$
8. 2-Chloropyrimidine § ...	$3{\cdot}34 \times 10^{-4}$	3·52	12,400	11,800	34·3	2$\frac{3}{3}$
9. 4-Chloropyrimidine § ...	$1{\cdot}5 \times 10^{-3}$	4·2	~10,500	~9,900	~35·7	2$\frac{3}{3}$

* Values calculated from Arrhenius parameters given to 2 significant figures. Values of E, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ are usually within the limits indicated in Table 3.

† Ref. 4*d*.

§ Ref. 19.

insoluble, 5-chloroacridine shows regular kinetics in reaction with piperidine,[4b] but rising coefficients when the reaction is conducted in ethanol in which the acidic piperidinium chloride is soluble.

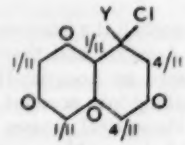
In Tables 3 and 4 are assembled results whereby the theoretical treatment of reactions of this type by Longuet-Higgins [1] may be tested quantitatively. In this treatment, which is based on the molecular-orbital method, it is assumed that the structure of the transition state is of the type shown in formula (I), *i.e.*, the localisation approximation for the study of chemical reactivity is adopted, and the carbon atom at the seat of substitution is assumed to be sp^3 hybridised. Changes in skeletal energy and in energy of interaction of the chlorine atom with the ring on formation of the transition state are neglected, so that only changes in unsaturation energy are to be determined. We consider the reactions with a given reagent under fixed conditions of a parent chlorohydrocarbon (iso-conjugate hydrocarbon), which is referred to by superscript zero, and of a chloroazahydrocarbon, and determine the difference in unsaturation energy of the initial and the transition state in each case. This gives the difference in *potential* energy of activation, *i.e.*, heat of activation referring to the absolute zero and the gas phase, for the two reactions, $(\Delta U - \Delta U^0)$.

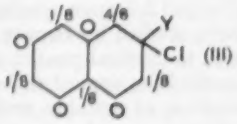
It has been shown by Longuet-Higgins [1] that if E_u and E^0_u represent the unsaturation energies of an azahydrocarbon and the iso-electronic hydrocarbon respectively, then $E_u - E^0_u = \sum_r \alpha_r q^0_r$ where q^0_r is the π-electronic charge at position r in the hydrocarbon and α_r is the coulomb term at position r in the azahydrocarbon. Applying this result differentially to the initial and transition states, and designating the latter by primes, we obtain :

$$\Delta U - \Delta U^0 = (E_u' - E_u) - (E^0_u' - E^0_u) = \sum_r \alpha_r (q^0_r' - q^0_r).$$

Now the initial states are even-alternant hydrocarbons or their aza-derivatives and the transition states are odd-alternant carbanions. Therefore q^0_r is unity at every position and $q^0_r' = 1 + c_r^2$, where c_r is a non-bonding molecular-orbital coefficient (Longuet-Higgins [1]). Hence $\Delta U - \Delta U^0 = \sum_r \alpha_r c_r^2$. Rules for the calculation of c_r have been given by Longuet-Higgins (*loc. cit.*). We regard α_r as an energy parameter for position r of the heteromolecule, taking the value δ at the position of aza-substitution and $\delta/3$ at neighbouring positions (auxiliary inductive parameter). The calculated charge-density distribution for substitution at the α- and the β-position in naphthalene is shown in (II) and (III) respectively. On this basis the values of $(\Delta U - \Delta U^0)$ shown in Tables 3 and 4 are readily calculated, *e.g.*, for reactions of 4-chloroquinoline $(\Delta U - \Delta U^0) = (4/11)\delta + (0)\delta/3 + (0)\delta/3 = 12\delta/33$.

(II)





(III)

It is usually assumed that for a series of reactions such as those listed in Tables 3 and 4, which are very similar in character, solvation factors are more or less constant throughout the series. In the absence of experimental evidence on this point, we shall make the same assumption. Then, provided that each series of reactions is characterised by an entropy of activation constant throughout the series (cf. Hammett [29]), it is legitimate to identify the potential-energy magnitudes $(\Delta U - \Delta U^0)$ with differences in the heats of activation, $\Delta H^\ddagger$. Constancy of entropy of activation is a prime assumption of the theoretical treatment, the validity of which may be judged from the values of $\Delta S^\ddagger$ in Tables 3 and 4. It is clear that the reactions of piperidine show comparatively small variations of $\Delta S^\ddagger$, and it is regrettable that a wider range of reactions could not be studied

[29] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 118.

because of the intervention of acid catalysis (cf. p. 1567). The reactions of ethoxide ions, even if unactivated or weakly activated substitutions are neglected, show so wide a range of values of $\Delta S^{\ddagger}$ as to render the above conditions inapplicable on the whole. As to values of $\Delta H^{\ddagger}$, the theoretical predictions are not borne out precisely by experiments, as can be seen from the tabulated values, although the prediction of equality of values of $\Delta H^{\ddagger}$ for reactions 4 and 5 (Table 3) is approximately true.

Polanyi and Evans have shown [30] that, when $\Delta S^{\ddagger}$ is not constant, log k for ordinary temperatures reflects trends in heats of activation at the absolute zero, better than does $\Delta H^{\ddagger}$. Fig. 3 illustrates the applicability of this to reactions 6—10 of Table 3, and over this limited range the theory appears, on this basis, to have semiquantitative validity. For the remaining reactions correlation between $(\Delta U - \Delta U^0)$ and log k/k_0 is poor. Despite the demonstrable inadequacy of the theory quantitatively, it leads to qualitative conclusions as to reactivity well supported by experiments, *e.g.*, the following reactivity

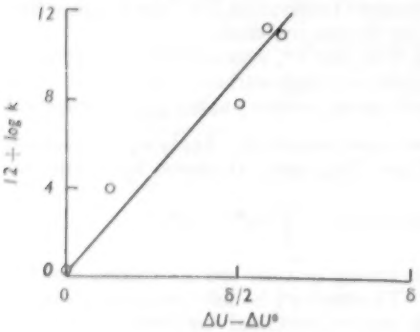


FIG. 3. *Relation between* log k *and* $(\Delta U - \Delta U^0)$ *for reactions of 2-chloro-mono- and -di-azanaphthalenes with ethanolic ethoxide.*

series: 4-chloroquinazoline > 1-chlorophthalazine ~ 4-chlorocinnoline ≫ 4-chloroquinoline ~ 1-chloro*iso*quinoline ≫ 1-chloronaphthalene. More elaborate treatments of the problem of reactivity in heterocyclic molecules by Brown [31] and by Dewar [32] seem to have no advantage over that at present being tested, in the first case for lack of necessary values for the parameters introduced.

Consideration of reactions 6 and 7 (Table 3) shows clearly that 3-chloro*iso*quinoline resembles 2-chloronaphthalene closely in properties and may be regarded, as the theory indicates, as virtually unactivated, in strong contrast with 1-chloro*iso*quinoline and 2-chloroquinoline.

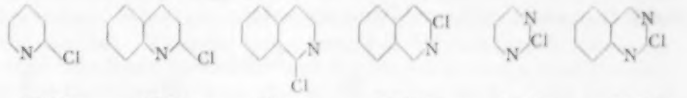
The solvolysis of 1- and 2-bromonaphthalene and all the isomeric monobromoquinolines by piperidine has been studied by Brower and Amstutz and their co-workers,[4b] and the results compared with theoretical predictions based on Longuet-Higgins's theory, which, however, has apparently been applied without taking into account the auxiliary inductive parameter. Examination of suitably revised theoretical figures and the experimental values shows that there is very fair agreement between theory and practice in the less activated cases (cf. Chapman,[2b] Table 1, p. 161).

It seems true that Longuet-Higgins's theory suffers from two main weaknesses: first, the assumption of the same completely localised structure for the transition state in all cases—there are probably considerable variations depending on the character of the nucleophilic reagent and of the compound undergoing substitution; and, secondly, the assumption of constancy of entropy of activation throughout. Moreover the value assigned to the so-called auxiliary inductive parameter remains rather arbitrary. Finally, despite the possibility of minor complications due to a primary steric effect, piperidine appears to be a more suitable nucleophilic reagent than ethoxide ion for experimental studies aimed at

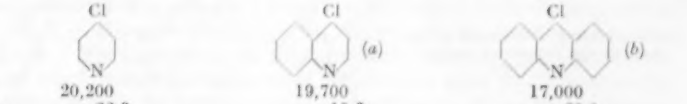
[30] Polanyi and Evans, *Trans. Faraday Soc.*, 1936, **32**, 1333.
[31] Brown, *J.*, 1951, 1955.
[32] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.

verifying the theory. It should be added that, on the whole, the localisation approximation leads to more accurate qualitative conclusions than the isolated molecule approximation, for the different charge density distributions in pyridine, quinoline, and *iso*quinoline calculated by Longuet-Higgins and Coulson [33] and by Brown and Dewar [34] both lead to conclusions unsupported by experiment.

TABLE 5.



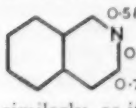
(i)	$\Delta H^{\ddagger}$ (cal. mole^{-1})	26,200	22,400	21,800	31,600	16,300	16,200
	$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	9·2	10·7	12·3	0·7	15·7	15·9
	$11 + \log_{10} k_{20}$	2·34	4·80	4·84	0·07	8·23	8·47
(ii)	$\Delta H^{\ddagger}$ (cal. mole^{-1})	19,100	14,900	13,800	—	11,800 *	10,500
	$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	35·8	38·9	41·9	—	34·3 *	37·8
	$10 + \log_{10} k_{20}$	0·28	3·18	3·40	—	6·47	6·63



(i)	$\Delta H^{\ddagger}$ (cal. mole^{-1})	20,200	19,700	17,000
	$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	22·3	19·6	20·0
	$9 + \log_{10} k_{20}$	1·94	2·81	4·79

(i) Reactions of ethoxide ion. (ii) Reactions of piperidine. * Part III.[19]

In Table 5 are collected results illustrating the effect of " fusing a benzene ring " (in fact, adding the system –CH:CH·CH:CH–) to the pyridine or the pyrimidine ring. This fusion can be done in the **5** : **6**-, **3** : **4**-, or **4** : **5**-position of 2-chloropyridine and generally results in an increase in activation of the mobile halogen, which can be regarded as due to the possibility of a wider delocalisation of the charge imposed on the transition state. However, the fusion which converts 2-chloropyridine into 3-chloro*iso*quinoline results in an unmistakable decrease in reactivity. This we ascribe to bond-fixation in the **2** : **3**-position of 3-chloro*iso*quinoline (as in naphthalene) with the result that the activating influence of the hetero-nitrogen atom is poorly transmitted to the 3-position in *iso*quinoline. This is supported by calculations of the mobile bond orders in *iso*quinoline,[35] as shown inset. Such an effect would not operate with 2-chloroquinoline or 1-chloro*iso*quinoline. It is probable that the comparatively low reactivity of 2-chloroquinazoline relatively to 2-chloropyrimidine is to be explained similarly, as it may be supposed that any increase of reactivity due to fusion of a benzene ring is offset by the reduction in the activating power of $N_{(3)}$ because of bond fixation. 4-Chloroquinazoline, on the other hand, where such an effect would not apply, is notably more reactive than 4-chloropyrimidine. The higher reactivity of 2-chloroquinoxaline than of 2-chloroquinazoline (Table 3) is also possibly to be understood in such terms. The powerful effect of fusion of a second benzene ring is also illustrated in Table 5 [reactions (*a*) and (*b*)]. This process of fusion or " annelation " of a benzene ring has been treated theoretically by Brown,[31] but it is questionable whether the theory is applicable to the present case, and the relevant parameters are not available.

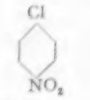
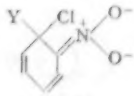


In conclusion, we provide in Table 6 further evidence for the view previously expressed [23] that a " *para* "-cyclic nitrogen atom and a *para*-exocyclic nitro-group are roughly equal in activating power, but that in the *ortho*-position the nitro-group is much more effective. Further, some of the results at present reported (Table 3, nos. 2 and 8, and **11** and **12**; Table 4, nos. 3 and **6**, and 8 and **9**; and Table 6) support the view that a transition state

[33] Longuet-Higgins and Coulson, *J.*, 1949, 971.
[34] Brown and Dewar, *J.*, 1953, 2406.
[35] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87.

with a predominating "*para*"-resonance structure is more stable than one with a predominating "*ortho*"-resonance structure. They also establish for the examples considered a reactivity sequence: *para* > *ortho*. Application of valence-bond theory to nucleophilic aromatic substitution by Green [36] has led to the order of reactivity, *ortho* > *para* > *meta*. When the results adduced by Green in support of his theoretical conclusions and the present results are considered as a whole, the balance of evidence favours the reactivity sequence, *para* > *ortho*, and the long-held view that a "*p*-quinonoid" is more stable than an "*o*-quinonoid" transition state.

TABLE 6.

				
$\Delta H^{\ddagger}$ (cal. mole^{-1})	23,000	26,200	19,400 *	20,200
$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$) ...	10·8	9·2	19·5 *	22·3
$10^6 k_{25}$ (l. mole^{-1} sec.$^{-1}$)	180	2·2	910	87
Predominating resonance structure in the transition state. Y = OEt				

* Bevan [37]

We thank the Department of Scientific and Industrial Research for a maintenance grant (to D.Q.R-H.), the Chemical Society for a grant for materials, Imperial Chemical Industries Limited for a grant for microanalyses and chemicals, and Merck and Co., Inc., for a gift of 2-chloroquinoxaline.

THE UNIVERSITY, SOUTHAMPTON. [*Received, November 14th*, 1955.]

[36] Green, *J.*, **1954**, 3538.
[37] Bevan, *J.*, **1951**, 2340.

313. *Organic Reactions in Sulphuric Acid. Part I. Ester Hydrolysis.*

By J. A. LEISTEN.

It is shown that, in the hydrolysis by sulphuric acid of methyl, ethyl, and *iso*propyl benzoate, the change of mechanism which occurs between the ethyl and the *iso*propyl ester [1] is from $A_{AC}1$ to $A_{AL}1$. A cryoscopic method is described for measuring rates of reactions in sulphuric acid solutions.

THE rate of hydrolysis of alkyl benzoates has been shown to vary as follows: methyl > ethyl < *iso*propyl < *tert.*-butyl.[1] The fact that the rate passes through a minimum suggests that a change of mechanism occurs in the middle of the series. This change of mechanism has been variously interpreted,[2] but on the basis of very little experimental evidence. In the present work evidence has been obtained by studying the hydrolysis of esters under varied experimental conditions, and in particular by finding the effect of polar substitution on the rate.

(1) *Evidence for the Unimolecular Hydrolysis of Methyl Benzoate.*—Graham and Hughes [3] found that the hydrolysis of methyl benzoate is of zero order with respect to water in 98—99·9% aqueous sulphuric acid. They concluded that the reaction is unimolecular. Newman, Craig, and Garrett [2b] have suggested, however, that the reaction is bimolecular, proceeding through an attack on the conjugate acid of the ester by the bisulphate ion.

[1] Kuhn, *J. Amer. Chem. Soc.*, **1949**, **71**, 1575.
[2] (*a*) Ref. 1; (*b*) Newman, Craig, and Garrett, *ibid.*, p. 869; (*c*) Gillespie and Leisten, *Quart. Reviews*, **1954**, **8**, 40.
[3] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, **1953**, p. 771.

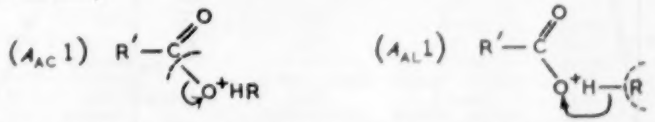
The rate of the hydrolysis has been measured cryoscopically in aqueous and in 100% sulphuric acid, and in dilute oleum. Expts. 1—3 (Table 1) show that the first-order rate constant is almost independent of the initial concentration of the ester, and therefore of the bisulphate ion, since methyl benzoate ionises as a strong base in sulphuric acid, according to equation (1) :[2b]

$$Ph{\cdot}CO_2Me + H_2SO_4 = Ph{\cdot}CO_2MeH^+ + HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

These results therefore eliminate the possibility of a rate-determining attack by the bisulphate ion. (A large increase in the concentration of ester reduces the rate, presumably through its effect on the medium. Thus the rate constant at 20°, calculated from these results, is 15% higher than that found by Graham and Hughes,[4] who used a concentration of ester approximately five times greater than that in the present work.) The rates are similar in 100% and in aqueous sulphuric acid; the rate is actually greater in oleum (Expts. 2, 4, and 6), emphatically confirming that water is not involved in the rate-determining step.

The present work thus supports the conclusion that the hydrolysis of methyl benzoate in sulphuric acid is unimolecular.

(2) *Polar Effects on Ester Hydrolysis in Sulphuric Acid.*—The effect of polar substituents on the rate of hydrolysis of esters has been predicted by Day and Ingold.[5] For acid-catalysed unimolecular hydrolysis it is necessary to estimate the effect both on the position of the equilibrium $R'{\cdot}CO_2R + HA \rightleftharpoons R'{\cdot}CO_2RH^+ + A^-$ and on the heterolysis of the conjugate acid of the ester. For most esters in sulphuric acid, however, this equilibrium lies far to the right-hand side,[2c] and so the influence of substitution must be confined to the heterolysis stage. For this reason, in sulphuric acid and all media of similar or greater acidity, substitutive effects should differ considerably from those predicted by Day and Ingold both for acyl–oxygen fission (the $A_{AC}1$ mechanism) and for alkyl–oxygen fission (the $A_{AL}1$ mechanism) :



Electron-donating substituents in R′ should aid, and in R retard, $A_{AC}1$ heterolysis but have the opposite effects on $A_{AL}1$ heterolysis. Electron-attracting substituents in R′ should retard, and in R aid, $A_{AC}1$ heterolysis but again have contrary effects in the $A_{AL}1$ case.

The influence on the rate of hydrolysis of methyl benzoate of each of these four types of substitution is known. Graham and Hughes [3] found the rate of hydrolysis of methyl *p*-toluate to be four times that of methyl benzoate, and concluded that the mechanism is $A_{AC}1$. This conclusion follows equally from Day and Ingold's discussion of substitutive effects and from the present one. Qualitative comparisons of rate have been made for a large number of esters by Kuhn and Corwin,[6] and, recently, by Bradley and Hill,[7] with no clear interpretation of the results. In fact, all these results * show the effects predicted above for the $A_{AC}1$ mechanism, thereby substantiating the present approach to polar effects on ester hydrolysis in sulphuric acid, as well as providing evidence for the mechanism of hydrolysis of methyl benzoate.

The effect of polar substitution on the hydrolysis of ethyl and *iso*propyl benzoate has been determined previously in only one case : Kuhn [1] compared qualitatively the rates of hydrolysis of these esters and their *p*-methoxy-derivatives. It was later shown that such derivatives are sulphonated rather rapidly in sulphuric acid,[8] and since, in addition, the polar effect of the free methoxy-group is the reverse of that of the protonated group, conclusions cannot be drawn from these results.

* See also Table 2, in which the rates of hydrolysis of methyl benzoate, methyl *p*-nitrobenzoate, and ethyl benzoate are compared at 65°.

[4] Personal communication; cf. Graham, Thesis, London, 1943.
[5] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[6] Kuhn and Corwin, *J. Amer. Chem. Soc.*, 1948, **70**, 3370.
[7] Bradley and Hill, *ibid.*, 1955, **77**, 1575.
[8] Newman and Deno, *ibid.*, 1951, **73**, 3651.

The rates of hydrolysis of ethyl benzoate and its *p*-nitro-derivative have been determined cryoscopically. The rate constant for ethyl *p*-nitrobenzoate and an extrapolated value for ethyl benzoate are compared at 65° in Table 2. The rates of hydrolysis of *iso*propyl benzoate and *p*-nitrobenzoate have been measured under identical conditions, in this case semiquantitatively (Table 2). Whereas the introduction of the *p*-nitro-group into ethyl benzoate leads to a sixty-fold *decrease* in rate, yet in the case of *iso*propyl benzoate it leads to a two hundred-fold *increase*. The size of the effects is evidence that the reactions are not bimolecular ; [5] the directions of the effects provide evidence for acyl–oxygen fission in the case of ethyl benzoate, and for alkyl–oxygen fission in the case of *iso*propyl benzoate. *tert.*-Butyl benzoate should have a greater tendency to alkyl–oxygen fission than *iso*propyl benzoate : accordingly, it has the greater rate of hydrolysis in sulphuric acid.[1] Moreover, *tert.*-butyl esters have been shown to be hydrolysed by the $A_{AL}1$ mechanism in other solvents.[9] Thus the change of mechanism in the hydrolysis of this series of esters is from

FIG. 1. *The change of i-factor with time in the hydrolysis of methyl benzoate.*

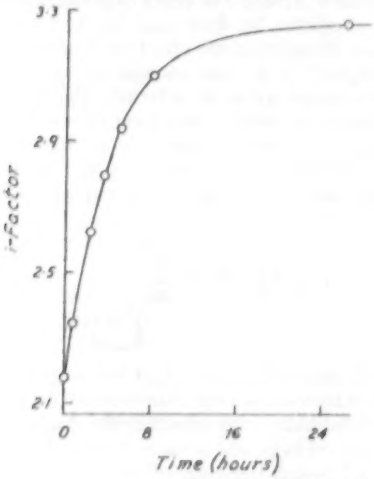
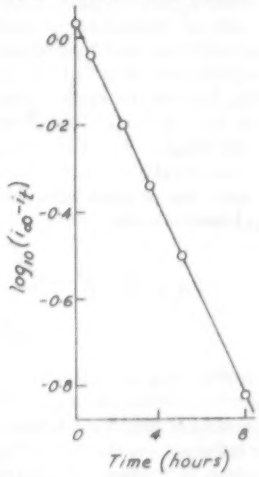


FIG. 2. *The cryoscopic determination of the rate constant.*



Both graphs relate to Expt. 3 (Tables 1 and 3).

$A_{AC}1$ in the case of methyl and ethyl benzoate, to $A_{AL}1$ in the cases of *iso*propyl and *tert.*-butyl benzoate.

It is reasonable to suppose that suitable substitution in ethyl or *iso*propyl benzoate might lead to changes in the mechanism of hydrolysis. It is possibly significant in this connection that, whereas hydrolysis of methyl benzoate is faster than that of ethyl benzoate, the reverse is true of the *p*-nitro-derivatives.

(3) *Instability of the Benzoyl Ion in Sulphuric Acid.*—The $A_{AC}1$ mechanism for the hydrolysis of methyl benzoate requires that the rate-determining step should be

$$Ph{\cdot}CO_2MeH^+ = Ph{\cdot}CO^+ + MeOH$$

The question arises whether the benzoyl ion remains as such, or whether it extracts water from the solvent to form the benzoic acidium ion, *i.e.*, whether the overall reaction is correctly represented by equation (2) or by equation (3) :

$$Ph{\cdot}CO_2Me + 3H_2SO_4 = Ph{\cdot}CO^+ + H_3O^+ + 2HSO_4^- + MeHSO_4 \quad . \quad . \quad . \quad . \quad (2)$$

$$Ph{\cdot}CO_2Me + 2H_2SO_4 = Ph{\cdot}CO_2H_2^+ + HSO_4^- + MeHSO_4 \quad . \quad . \quad . \quad . \quad . \quad (3)$$

A previous experiment to determine this led to an equivocal result.[2b]

[9] Bunton and Wood, *J.*, 1955, 1522; Stimson, *J.*, 1955, 2010, 2673.

Fig. 1 shows the change of the *i*-factor with time at constant temperature of methyl benzoate in sulphuric acid, in a typical experiment. The *i*-factor approaches a limiting value of approximately 3, and analysis of the solution shows that at this stage hydrolysis is complete (see Table 3). These results together show that the overall reaction is according to equation (3). The fact that the cryoscopic method yields a rate constant when the solvent is oleum confirms this conclusion, for a reason that is explained below (p. 1576).

This evidence for the instability of the benzoyl ion is similar in type to that provided by a recent study of the behaviour of benzoic anhydride in sulphuric acid,[10] but is perhaps more convincing in that the formation of the benzoyl ion as a reaction intermediate has been better demonstrated in the present case.

Results

TABLE 1. *The rate of hydrolysis of methyl benzoate in sulphuric acid and oleum.*

	Molality					Molality			
Expt.	H_2O	Ester	Temp.	k_1 (hr.$^{-1}$)	Expt.	H_2O	Ester	Temp.	k_1 (hr.$^{-1}$)
1	0·068	0·0231	25·1°	0·255	—	0·078	0·485	20·0°	0·095 *
2	0·069	0·0869	25·1	0·250	2, 5	0·068—	0·0869—	20·0	0·111 †
3	0·065	0·1830	25·1	0·247		0·069	0·0902		
4	0·00	0·0927	25·1	0·255		SO_3	Ester		
5	0·068	0·0902	34·55	1·046	6	0·074	0·0513	25·1	0·357

* This result was obtained by Graham and Hughes.[4]

† Calculated from the results of Expts. 2 and 5, Arrhenius temperature dependence being assumed.

TABLE 2. *The rate of hydrolysis of esters in aqueous sulphuric acid.*

		Molality			
Expt.	Ester	H_2O	Ester	Temp.	k_1 (hr.$^{-1}$)
7	Ethyl benzoate	0·071	0·0848	25·1°	0·0854
8	Ethyl benzoate	0·067	0·0794	34·55	0·403
2, 5	Methyl benzoate	0·068—0·069	0·0869—0·0902	64·0	52·4
9	Methyl *p*-nitrobenzoate	0·066	0·0863	64·0	0·277
7, 8	Ethyl benzoate	0·067—0·071	0·0794—0·0848	64·0	29·0
10	Ethyl *p*-nitrobenzoate	0·066	0·0807	64·0	0·456
11	*iso*Propyl benzoate	0·068	0·23	9	0·6 *
12	*iso*Propyl *p*-nitrobenzoate	0·068	0·23	9	120 *

* Approximate values.

TABLE 3. *Summarised cryoscopic results.**

Expt.	Initial *i*-factor	Time (hr.)	Final *i*-factor	i_∞	Expt.	Initial *i*-factor	Time (hr.)	Final *i*-factor	i_∞
1	1·93	21·2	3·01	2·99	6	0·79	22·4	1·81	1·80
2	2·02	—	—	3·06	7	2·04	—	—	3·08
3	2·17	26·0	3·26	3·25 †	8	2·03	20·0	3·07	3·05
4	2·06 ‡	27·2	3·13	3·10	9	1·77	28·8	2·88	2·86
5	2·03	7·7	3·07	3·04	10	1·91	17·8	3·45	3·00 §

* The "Final *i*-factors" in col. 4 are experimentally determined infinity values recorded after periods of reaction given in col. 3. The values of i_∞ (col. 5) are those which lead to the best first-order plots. Other information concerning these experiments is in Tables 1 and 2.

† 98·7% (± 2%) of the theoretical yield of benzoic acid was found by analysis of the solution at the end of this run.

‡ A hypothetical value (10·43°) of the freezing point of the solvent was chosen to give an initial *i*-factor consistent with those found in aqueous sulphuric acid.

§ This value was chosen by reference to Expt. 9, and the rate constant was determined from the earlier freezing-point measurements. Ethyl hydrogen sulphate is clearly somewhat unstable in sulphuric acid at 65°.

Experimental

Materials.—Commercial samples of methyl, ethyl, and *iso*propyl benzoate were distilled *in vacuo*: the fractions used boiled over a 1° range. Methyl *p*-nitrobenzoate (m. p. 95—95·5°), ethyl *p*-nitrobenzoate (m. p. 56°), and *iso*propyl *p*-nitrobenzoate (m. p. 105—106°) were purified by washing ethereal solutions with aqueous alkali and recrystallising the solids from ethanol.

[10] Leisten, *J.*, 1955, p. 298.

Determination of Reaction Rates from Freezing-point Measurements.—Cryoscopic determination of reaction rates in sulphuric acid depends upon the fact that the freezing point of a sulphuric acid solution varies in an almost linear way with the number of solute particles in the solution. The method is widely applicable to the study of reactions in sulphuric acid,[11] and will be illustrated by reference to the hydrolysis of methyl benzoate. The rate constants in Table 1 were obtained by plotting the logarithm of $(i_\infty - i_t)$ against time, where i_∞ is the i-factor corresponding to complete reaction and i_t the i-factor after the solution has been at the reaction temperature for a time t. Fig. 2 is a typical plot. It is seen by reference to equations (1) and (3) that in the course of the reaction the conjugate acid of the ester is replaced by that of benzoic acid, a process which should not lead to appreciable change of freezing point: at the same time a molecule of the non-electrolyte methyl hydrogen sulphate is produced. Thus from the beginning to the end of the hydrolysis the i-factor should increase by $1{\cdot}0 \pm 0{\cdot}1$, the uncertainty arising from the fact that the number of particles per solute molecule may differ from the i-factor by as much as 10%. In the present work the value of i_∞ chosen to give the best first-order plot varied from 1·01 to 1·08 above that of the initial i-factor. The experimental value of i_∞ (recorded after approximately ten times the half-life of the reaction) varied from 1·02 to 1·09 above the initial i-factor. The fact that the optimum values of i_∞ are close both to the experimental values and to those predicted from the stoicheiometry of the reaction shows that for suitable reactions the method is sound. In a typical case (Expt. 4) the use of a value of i_∞ 0·01 above the optimum led to a rate constant only 1·3% lower than that recorded. The method is simple to operate, avoids analytical difficulties, and requires only small concentrations of solute. There are a number of limitations. The reaction must be negligibly slow in the temperature region in which the freezing-point measurements are made (5—10°), and must lead to stable products: *e.g.*, *iso*propyl esters cannot be studied in this way since the *iso*propyl hydrogen sulphate formed undergoes further slow reactions.[12] It is of course necessary that the reactions be accompanied by a change in the number of solute particles: when the solvent is oleum, this change must be in the number of solute *molecules*, and the number of *ions* must remain the same, because in oleum only non-electrolytes produce a nearly linear depression of the freezing point.[13] We have already seen that hydrolysis according to equation (3) satisfies this last condition, and should therefore expect to observe first-order kinetics in the hydrolysis of methyl benzoate in oleum when studied by the cryoscopic method: that this is in fact found is a further verification of equation (3).

The cryoscopic technique and the method of computing i-factors have been previously described.[14] After the initial freezing-point determination the solution was heated rapidly to the reaction temperature by placing the cryoscope in a water-bath at 10° above this temperature. The cryoscope was then transferred to a thermostat. After the required interval of time the solution was rapidly chilled and the freezing point re-determined. For the runs at 65°, the thermometer was replaced by a ground-glass stopper between measurements: the thermometer was rinsed, dried with filter-paper, and stored over anhydrous magnesium perchlorate.

Estimation of Benzoic Acid in Sulphuric Acid.—20 ml. (36·71 g.) of the crysocopic solution (from Expt. 3) were pipetted on to 35 g. of ice in a 100 ml. tall-form beaker immersed in a freezing mixture. The liquid was removed with a filter stick, and the wet precipitate of benzoic acid transferred to a 500 ml. wide-necked flask with hot water. Excess of barium chloride was added to replace the sulphuric acid in the mixture by hydrochloric acid, and the volume was made up to 200 ml. with distilled water. The solution was titrated conductometrically with 0·5N-ammonia. The weight of benzoic acid thus found was 0·768 g. The solubility loss was estimated [15] at 0·022 g. This correction being applied, the weight found was 0·790 g., corresponding to 98·7% hydrolysis. The uncertainty of this result is mainly that of the solubility correction. It was found that this estimation cannot be performed gravimetrically, because in freeing the precipitate from sulphuric acid considerable loss of benzoic acid occurs. The mixture of benzoic acid and sulphuric acid cannot be titrated directly because the sulphuric acid branch of the neutralisation curve is not linear, probably on account of the rather weak second dissociation of sulphuric acid.

Semiquantitative Rate Measurements.—2 ml. of sulphuric acid at 9° were added to each tube

[11] Leisten, unpublished experiments.
[12] Oddo and Scandola, *Gazzetta*, 1909, **39**, 1.
[13] Gillespie, *J.*, 1950, 2516.
[14] Gillespie and Leisten, *J.*, 1954, 1.
[15] Hammett and Chapman, *J. Amer. Chem. Soc.*, 1934, **56**, 1282; "Handbook of Chemistry and Physics," Chemical Rubber Publ. Co., Cleveland, Ohio, 1948, p. 666.

containing the required amount of ester, the tube being immersed in a thermostat at 9°. The ester was dissolved by stirring. The tube was withdrawn after the required interval of time and the contents were poured on an equal weight of ice cooled by solid carbon dioxide. The mixture was filtered. In the case of *iso*propyl benzoate the size of the benzoic acid precipitate on the filter paper was compared visually for different times of reaction :

Time of reaction (min.)	15	30	70	∞
Relative size of ppt.	1	2	4	8
Estimated half-life	70 min.			

In the case of *iso*propyl *p*-nitrobenzoate, the precipitate obtained by pouring the reaction mixture on ice was treated with alkali to separate the ester from the acid. The acid was then re-precipitated by acidification. The amounts of both ester and acid were compared visually : by this means the half-life was estimated to be 20 sec.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 21st*, 1955.]

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314. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part III.* Further Investigations of the Hofmann Degradation.*

By A. R. PINDER.

The base $C_{13}H_{21}N$, obtained by Hofmann degradation of dioscorine, breaks down when heated with palladised charcoal into trimethylamine, an unidentified base, and *iso*butylbenzene or ββ-dimethylstyrene, depending on the activity of the catalyst. Hofmann decomposition of the base $C_{13}H_{21}N$ gives a hydrocarbon $C_{11}H_{14}$, which is not aromatic. Spectral measurements on these degradation products and compounds derived from them are reported. The degradative work has been complicated by the formation of mixtures.

The structure (XIII) is tentatively proposed for dioscorine.

IN previous parts [1,2] of this Series reasons were given for believing that the alkaloid occurring in the tubers of *Dioscorea hispida*, Dennst., is dioscorine, obtained by Gorter [3] from tubers of *Dioscorea hirsuta*, Blume. The present communication presents more evidence for this view, and henceforward it is assumed that the two bases are identical.

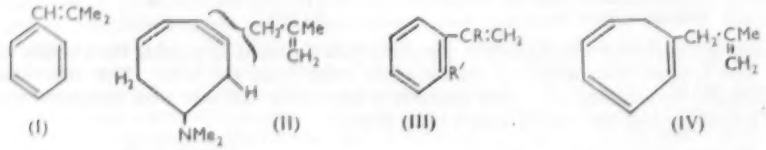
Further investigations on the structure of dioscorine are now reported. In the Hofmann degradation of the alkaloid [2] it has been found more convenient to use an ion-exchange resin for conversion of dioscorine methiodide into the methohydroxide, and this procedure has resulted in a slightly improved yield of the Hofmann base, $C_{13}H_{21}N$. A closer examination of the infrared absorption of this base confirms that it is not an aromatic amine (no bands characteristic of the benzene ring in the 1660—2000 cm.$^{-1}$ region), and strong bands at 891, 1415, and 3090 cm.$^{-1}$ confirm [4] the presence of a methylene group of the type $R_1R_2C{:}CH_2$. The general shape of the infrared curve supports the view expressed previously [2] that the base is a mixture of isomers, but attempts to separate them by adsorption methods failed.

When the base $C_{13}H_{21}N$ was heated at 210—220° with a freshly prepared palladised charcoal catalyst, it broke down smoothly into trimethylamine, a base, and a hydrocarbon, $C_{10}H_{14}$, mainly *iso*butylbenzene. The first and the last product were recognised as the picrate and *o*-aroylbenzoic acid derivative respectively. The base, b. p. 110—111°/12·5 mm. (picrate m. p. 144°), is now under investigation. If a somewhat less active catalyst was used, the basic products were the same, but a hydrocarbon $C_{10}H_{12}$ was obtained : this was mainly ββ-dimethylstyrene (*iso*but-1-enylbenzene) (I), recognised by

* Part II, *J.*, 1953, 1825.

[1] Pinder, *J.*, 1952, 2236.
[2] *Idem*, *J.*, 1953, 1825.
[3] Gorter, *Rec. Trav. chim.*, 1911, **30**, 161.
[4] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954.

oxidation to benzaldehyde and acetone, by reduction in the presence of nickel to *iso*butylbenzene, and as its crystalline nitrosite, m. p. 124—125° (decomp.). The nitrosite of ββ-dimethylstyrene has been variously reported [5] as having a m. p. ranging from 112° to 156°. An authentic specimen of the hydrocarbon was therefore synthesised from benzaldehyde. It formed a nitrosite, m. p. 124—125° (decomp.), alone or mixed with the nitrosite of the hydrocarbon obtained from dioscorine.



(I) (II) (III) (IV)

The infrared absorption curve of the hydrocarbon $C_{10}H_{14}$ was almost identical with that of authentic *iso*butylbenzene, but it was evident that traces of other hydrocarbons were present. The ultraviolet absorption of the hydrocarbon $C_{10}H_{12}$ showed a wide maximum at 255 mμ (ε 11,850), the position and intensity of which varied somewhat with different specimens. This is at a slightly higher wavelength than that for ββ-dimethylstyrene ($\lambda_{max.}$ 240 mμ; ε 8500), and it is concluded that the hydrocarbon $C_{10}H_{12}$ is contaminated with non-aromatic, conjugated hydrocarbons, which absorb at higher wavelengths. The hydrocarbon $C_{10}H_{14}$ showed a peak at 240 mμ (ε 835), which may be due to a substituted styrene.[6]

The formation of *iso*butylbenzene and ββ-dimethylstyrene from the base $C_{13}H_{21}N$ suggests strongly that the latter has a seven-membered carbon ring, and this and earlier evidence [2] support the view put forward by Gorter [3] that the base is a mixture of *iso*butenyl-*NN*-dimethyl*cyclo*heptadienylamines of structure (II), the isomers arising from the positions of the double bonds and of the alkenyl group. A structure such as (II) might be expected to lose a carbon atom and two allylic hydrogen atoms as trimethylamine, with the simultaneous formation of aromatic hydrocarbons. The ultraviolet absorption [2] of the base $C_{13}H_{21}N$ ($\lambda_{max.}$ 270 mμ; ε 17,500) suggests that in at least one of these isomers the three double bonds are conjugated. The strong $C{:}CH_2$ band in the infrared spectrum of the base, and the failure to obtain acetone as an ozonolysis product, indicate that the base contains only small amounts of isomers with a $Me_2C{:}CH-$ side-chain. Further, the base shows no band in the 790—840 cm.$^{-1}$ region, characteristic [4] of the grouping $RR'C{:}CHR''$.

The Hofmann degradation of the base $C_{13}H_{21}N$, already described by Gorter,[3] was next re-investigated. The base formed a partly crystalline methiodide,[2] which was converted by anion-exchange resin into a foamy methohydroxide. Decomposition of the latter gave trimethylamine and a highly unsaturated hydrocarbon $C_{11}H_{14}$, which corresponded exactly in properties with the hydrocarbon obtained by Gorter, although he gave no analytical figures. The hydrocarbon polymerised in a few hours, and on catalytic hydrogenation absorbed 4 mols. of hydrogen readily, to give a saturated hydrocarbon, $C_{11}H_{22}$. Gorter's statement that oxidation of the unsaturated hydrocarbon with permanganate gave only formic acid and no aromatic acid has been confirmed; a careful search did not reveal an aromatic acid. Ozonolysis gave formaldehyde, but no acetone. Gorter has described the hydrobromination, dehydrobromination, and oxidation of the hydrocarbon to *o*-toluic acid.

The infrared absorption of the hydrocarbon $C_{11}H_{14}$ suggested that it contained traces of aromatic hydrocarbons, weak bands in the 1600—2000 cm.$^{-1}$ region indicating the presence of a 1 : 2- or 1 : 3-di- or 1 : 2 : 3-tri-substituted benzene system, the 1 : 2-disubstitution being preferred. Bands at 890, 1633, 1785, and 3070 cm.$^{-1}$ confirm the presence of a $C{:}CH_2$ group, which is evidently of the type $RR'C{:}CH_2$. These observations could be explained by the presence of small amounts of *o* : ω-dialkylstyrenes (III; R =

[5] Angeli, *Ber.*, 1892, **25**, 1956; Blaise and Herman, *Ann. Chim.* (*France*), 1911, **23**, 522; Kishner, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 863; Tiffeneau and Orékhoff, *Bull. Soc. chim.* (*France*), 1921, **29**, 809; Haller and Ramart, *Compt. rend.*, 1922, **174**, 1212.

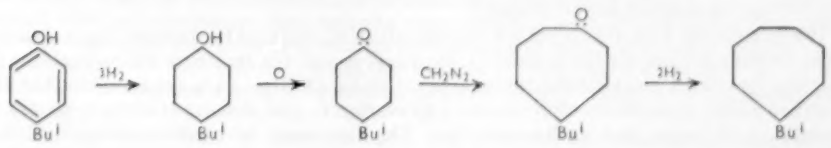
[6] Hirschberg, *J. Amer. Chem. Soc.*, 1949, **71**, 3241.

Me, R′ = Et, or *vice versa*). The ultraviolet absorption of the hydrocarbon $C_{11}H_{14}$ is, however, not in agreement with this. The product has two maxima, at 230 (ε 8500) and 278 mμ (ε 8500) (wide), the former being possibly an inflexion. The ultraviolet absorption of substituted styrenes of type (III) has been examined recently by Hirschberg.[6] *o* : α-Dimethylstyrene (III; R = R′ = Me), for example, shows no maximum absorption between 210 and 300 mμ, owing to steric hindrance between the *o*-substituents.

The most satisfactory explanation of the behaviour of the hydrocarbon $C_{11}H_{14}$ appears to be that it is a mixture, possibly containing a very small proportion of an *o* : α-dialkylstyrene, but is mainly an alkenyl*cyclo*heptatriene of possible structure (IV), which could be degraded by Gorter's procedure to *o*-toluic acid, and in which the positions of the double bonds are not fixed though at least three must be in conjugation. The strong evidence for the presence of a $C{:}CH_2$ group suggests that this bond may be fixed. *cyclo*Heptatriene [7] itself absorbs maximally at 260 mμ (ε not quoted), and a typical conjugated tetraene, decatetraenol,[8] at 299 mμ (ε 64,000).

The saturated hydrocarbon $C_{11}H_{22}$ shows infrared bands at 1154, 1170, 1366, and 1380 cm.$^{-1}$, characteristic of a $>CMe_2$ group. If the reasoning regarding the structure of the hydrocarbon $C_{11}H_{14}$ is correct, the infrared absorption curve of the saturated hydrocarbon should resemble that of *iso*butyl*cyclo*hexane,[9] and, indeed, a comparison of the two curves shows that they are very similar. An authentic specimen of *iso*butyl*cyclo*heptane (IX) was synthesised from *p-iso*butylphenol (V) by the route shown. The infrared absorption curves of the product (IX) and the hydrocarbon $C_{11}H_{22}$ were very similar, but not identical. A *C*-methyl estimation for the hydrocarbon $C_{11}H_{22}$ gave a value of 0·66 per molecule, which is more in agreement with structure (IX) than with structures derived by the total hydrogenation of the benzene derivative (III).

It is concluded from the investigations on the hydrocarbons derived from dioscorine



(V) (VI) (VII) (VIII) (IX)

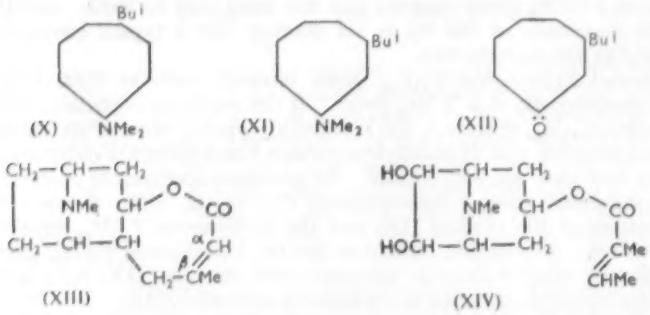
that, as first postulated by Gorter,[3] the alkaloid is an unsymmetrical derivative of tropane, and that the mixtures of products obtained are the result of the ability of the primary Hofmann degradation to take place in more than one direction. It is rather surprising that the final Hofmann product, the hydrocarbon, $C_{11}H_{14}$, is not aromatic.

The saturated base $C_{13}H_{27}N$, obtained [3] by hydrogenation of the Hofmann base $C_{13}H_{21}N$, has also been further examined. Its infrared absorption curve shows strong bands at 1156, 1179, 1364, and 1379 cm.$^{-1}$, characteristic of a $>CMe_2$ group. If the partial structure (II) assigned to the Hofmann base is correct, the base $C_{13}H_{27}N$ would be one of three possible *iso*butyl-*N*-dimethyl*cyclo*heptylamines. Two of these, (X) and (XI), have been synthesised for comparison. 4-*iso*Butyl-*NN*-dimethyl*cyclo*heptylamine (X) was obtained from the ketone (VIII) by reduction of its oxime, followed by methylation. The 3-isomer (XI) was obtained by a similar method from 3-*iso*butyl*cyclo*heptanone (XII), which was synthesised *via* the appropriate adipic and suberic acids (see Experimental section). The two bases had physical properties very similar to those of the base $C_{13}H_{27}N$, and the infrared absorption curves of all three bore a striking similarity. It was not possible to say, however, that the unknown base was identical with either of the synthetic bases. The synthetic bases formed crystalline methiodides, m. p. respectively 271° (decomp.) and 207°, neither of which appeared to be identical with the methiodide (m. p.

[7] Dryden, *J. Amer. Chem. Soc.*, 1954, **76**, 2841.
[8] Braude, *Ann. Reports*, 1945, **42**, 116, and references there cited.
[9] American Petroleum Institute, infrared curve no. 557.

182—183°) of the base $C_{13}H_{27}N$, although neither showed a m. p. depression on admixture with the unknown methiodide. It is not unexpected that isomers of such similar structure should have closely similar infrared absorption curves. The comparison may also be complicated by the fact that the structures (X) and (XI) can exist in *cis*- and *trans*-forms.

The oxidation of dioscorine with potassium permanganate has been investigated, the lactone ring being first opened by pre-treatment with alkali. The only non-nitrogenous product isolated was oxalic acid. No basic, ketonic material has been obtained, and efforts to isolate an amino-acid have so far proved unsuccessful. The isolation of oxalic acid is consistent with the view that the lactone ring in dioscorine contains the grouping $-O{\cdot}CO{\cdot}CH{:}C<$. The ultraviolet absorption of the alkaloid is also consistent with the



presence of this grouping ($\lambda_{max.}$ 217 mμ) (cf. ethyl β-methylcrotonate, $Me_2C{:}CH{\cdot}CO_2Et$,[10] $\lambda_{max.}$ 217 mμ), as pointed out previously.[2]

If it is assumed that dioscorine is a tropane alkaloid, and that the lactone ring is attached to the tropane system *via* the tropine (3-)hydroxyl group, the structure which explains the reactions described most satisfactorily appears to be (XIII). It is conceivable that this structure would break down on Hofmann degradation to give structures of the type (II), by elimination of water and carbon dioxide. The formation of oxalic acid on oxidation indicates that $C_{(\alpha)}$ is unsubstituted, and the ultraviolet absorption of the alkaloid, and the nature of the base $C_{13}H_{27}N$ and the hydrocarbons, suggest that a methyl group is at $C_{(\beta)}$. The structure is closely related to that of meteloidine [11] (XIV). It is interesting that the nitrogen atom is situated relatively to the carbonyl group in a very similar position to that which is found in dihydro-β-erythroidine,[12] and it will be recalled that the latter compound undergoes a similar type of Hofmann degradation.

Tests kindly carried out by Mr. A. W. Patterson, of the Heriot-Watt College, Edinburgh, have shown that dioscorine, in common with other lactones, has anthelmintic properties. Against *Ascaris lumbricoides* and *Fasciola hepatica* the alkaloid produced a marked depression, with slow recovery, at a dilution of 1 in 2000. There was no activity at a dilution of 1 in 4000.

Experimental

Ultraviolet absorptions were measured in MeOH solution.

Hofmann Degradation of Dioscorine.—The following are improved conditions for this degradation.[13] Dioscorine methiodide (3·3 g.) in water (25 c.c.) was passed down a column, about 20 cm. long, containing Amberlite IRA-400(OH) anion-exchange resin (10 g.). The column was eluted with water (30 c.c.), and the combined aqueous solutions were evaporated to dryness *in vacuo*. The methohydroxide so obtained was decomposed as previously described.[2] The crude distillate was taken up in ether and shaken several times with dilute hydrochloric acid.

[10] Ungnade and Ortega, *J. Amer. Chem. Soc.*, 1951, **73**, 1564.
[11] Heusner, *Chem. Ber.*, 1954, **87**, 1032.
[12] Boekelheide, Weinstock, Grundon, Sauvage, and Agnello, *J. Amer. Chem. Soc.*, 1953, **75**, 2550.
[13] Cf. Weinstock and Boekelheide, *ibid.*, p. 2546.

The combined acid extracts were rendered strongly alkaline with potassium hydroxide, and the solution was heated on the water-bath for 1 hr. The cooled solution was thoroughly extracted with ether, and the extracts were dried and evaporated. The Hofmann base distilled at 114—115°/10 mm. (0·7 g.) (Found: C, 81·5, 81·5; H, 10·7, 10·7; N, 7·1, 7·4. Calc. for $C_{13}H_{21}N$: C, 81·7; H, 11·0; N, 7·3%). Infrared absorption (liquid film): no benzene-ring bands in the 1600—2000 cm.$^{-1}$ region; $C(CH_3)_2$ bands at 890, 1415, and 3090 cm.$^{-1}$.

Decomposition of the Base $C_{13}H_{21}N$ *with Palladised Charcoal.*—(*a*) The pure base (2·0 g.) and freshly prepared palladised charcoal [14] (30%; 0·6 g.) were heated gradually under reflux in an oil-bath to 210—220°, the gases evolved being absorbed in cooled methanol. At 170—175° a brisk effervescence occurred; after 3 hr. at 210—220° the mixture was cooled, treated with ether, and filtered. The filtrate was washed twice with dilute hydrochloric acid, then with sodium hydrogen carbonate solution, and dried. The ether was evaporated through a short Vigreux column. The residue (1·3 g.) distilled mainly at 180—190°/769 mm. (0·5 g.); a smaller fraction (0·2 g.) had b. p. 190—200°/769 mm., and there was a residual, involatile tar (0·6 g.).

The main fraction, twice distilled through a micro-Vigreux column, had b. p. 124—125°/100 mm., n_D^{25} 1·4840 (Found: C, 89·6, 89·6; H, 10·3, 10·4. Calc. for $C_{10}H_{14}$: C, 89·6; H, 10·4%). Ultraviolet max.: 240 mμ (ε 835) (wide) and strong " end-absorption " at *ca.* 200 mμ. Infrared absorption (liquid film): almost identical with that of *iso*butylbenzene; [15] principal bands at 699, 740, 1170, 1370, and 1380 cm.$^{-1}$; weak bands in 890 and 1750—1800 cm.$^{-1}$ regions, due to impurities.

The hydrocarbon was stable to cold, acid potassium permanganate for several hours. It was converted into its *o-aroylbenzoic acid derivative*; the hydrocarbon (0·2 g.), powdered anhydrous aluminium chloride (0·4 g.), phthalic anhydride (0·2 g.), and dry carbon disulphide (10 c.c.) were refluxed on the water-bath for 1½ hr. The solvent was decanted and the residue decomposed with ice-cold 5N-hydrochloric acid (15 c.c.). The crude acid was collected and washed with water; it was dissolved in dilute aqueous ammonia (10 c.c.) and water (10 c.c.), and the solution boiled for a minute with a little charcoal. The filtered solution was cooled and acidified with 5N-hydrochloric acid, and the solid collected, washed with water, and dried. After two crystallisations from 60% ethanol the acid was obtained as rhombic prisms, m. p. 124·5° (Found: C, 76·5; H, 6·6. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). The m. p. was undepressed on admixture with an authentic specimen of *o*-(*p-iso*butylbenzoyl)benzoic acid (see below).

An authentic specimen of *iso*butylbenzene was prepared by Clemmensen reduction of *iso*butyrophenone.[16] It had b. p. 125°/100 mm. n_D^{20} 1·4865. It was converted into *o*-(*p-iso*butylbenzoyl)benzoic acid as described for the hydrocarbon $C_{10}H_{14}$. The acid separated from 60% ethanol in rhombic prisms, m. p. and mixed m. p. 124·5° (Found: C, 76·4; H, 6·3%).

The methanolic solution of the evolved vapours was mixed with an excess of methanolic picric acid, and the crystalline precipitate collected and recrystallised from ethanol. It formed yellow, elongated prisms, m. p. 221°, alone or admixed with trimethylamine picrate, m. p. 221°.

(*b*) The use of an older and less active specimen of palladised charcoal led to slightly different results. The two basic products appeared to be the same, but the hydrocarbon product, isolated in the same manner, had b. p. 76—77°/14 mm., 186°/760 mm., n_D^{20} 1·5415 (Found: C, 90·8; H, 9·0. Calc. for $C_{10}H_{12}$: C, 90·85; H, 9·15%). Ultraviolet max.: 255 mμ (ε 11,850) (wide) and strong " end-absorption " at *ca.* 200 mμ. The compound was oxidised readily to benzaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 237°) and acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°) by acid permanganate. When shaken in hydrogen in solution in ethanol at atmospheric pressure and temperature with " W2 " Raney nickel [17] it absorbed 1 mol. of hydrogen, giving *iso*butylbenzene, b. p. 174—175°, n_D^{20} 1·4866, which reacted with phthalic anhydride to give the corresponding *o*-aroylbenzoic acid (see above), m. p. and mixed m. p. 124—125°. The *nitrosite* was prepared [18] by shaking the hydrocarbon (0·1 g.), sodium nitrite (0·2 g.), water (3 c.c.), and glacial acetic acid (0·2 g.) for several hours at 0°. The crystalline precipitate was collected, washed with water, and dried; it crystallised from benzene in needles, m. p. 124—125° (decomp.) (Found: C, 57·4; H, 5·4; N, 13·4. Calc. for $C_{10}H_{12}O_3N_2$: C, 57·7; H, 5·8; N, 13·5%). An authentic specimen of ββ-dimethylstyrene

[14] Linstead and Thomas, *J.*, 1940, 1127.
[15] American Petroleum Institute, infrared curves nos. 188, 412.
[16] Hennion and Auspos, *J. Amer. Chem. Soc.*, 1943, **65**, 1603.
[17] *Org. Synth.*, Coll. Vol. III, p. 181; *Chem. Abs.*, 1953, **47**, 3098.
[18] Cf. Baeyer, *Annalen*, 1893, **278**, 88.

(I) was prepared from 2-methyl-1-phenylpropan-1-ol [19] by dehydration with oxalic acid.[20] The hydrocarbon, b. p. 185—186°, n_D^{20} 1·5410, was converted into its nitrosite as described above, giving needles (from benzene), m. p. 124—125° (decomp.) alone or mixed with the nitrosite from the hydrocarbon $C_{10}H_{12}$ (Found: C, 57·5; H, 5·5%).

Hofmann Degradation of the Base $C_{13}H_{21}N$.—A mixture of the base (3·75 g.), methanol (10 c.c.), and methyl iodide (6 c.c.) was kept overnight at room temperature, then evaporated to dryness *in vacuo*. The methiodide was partly crystalline and partly a glass; it was dissolved in water (60 c.c.) and passed down a column (about 15 cm.) containing Amberlite IRA-400(OH) anion-exchange resin (20 g.). After elution with water (50 c.c.) the aqueous solution was evaporated to dryness at 11 mm. from a bath at 40—45°. The foamy residue, which smelled strongly of trimethylamine, was decomposed by gentle heating with a free flame at 10—11 mm., the receiver being cooled to −10°. The crude distillate (1·6 g.) was taken up in ether and washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The ether was evaporated through a Vigreux column, leaving an oil which distilled at 83—84°/10·5 mm. (0·8 g.) (Found: C, 90·25, 90·3; H, 9·3, 9·4. $C_{11}H_{14}$ requires C, 90·4; H, 9·6%). Ultraviolet max.: 230 (inflexion, ε 8500) and 278 mμ (ε 8500). Infrared absorption (liquid film): bands at 741, 890, 1170, 1376, 1633, 1785, 2980, and 3070 cm.$^{-1}$. The *hydrocarbon* was very unstable, and polymerised in a few hours to a white gum, insoluble in ether. With a drop of concentrated sulphuric acid it polymerised vigorously to a dark, plastic mass. The hydrocarbon (0·67 g.) in glacial acetic acid (10 c.c.) was shaken with pre-reduced Adams platinum oxide in hydrogen. The uptake was 441 c.c. at 17°/755·7 mm. (theor. for $4H_2$: 439 c.c.). The solution was filtered, the filtrate diluted with a large volume of water, and the hydrocarbon isolated with ether. The ethereal extract was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated *via* a 30 cm. Vigreux column. The residual *hydrocarbon*, distilled at 68·5—69°/11 mm. (0·6 g.), had n_D^{17} 1·4480 (Found: C, 85·4, 85·6; H, 14·0, 14·1; *C*-Me, 6·4. $C_{11}H_{20}$ requires C, 85·7; H, 14·3; 1 *C*-Me, 9·7%). Infrared absorption (liquid film): bands at 1380, 1366, 1170 and 1154 cm.$^{-1}$; curve very similar to those of *iso*butyl*cyclo*hexane and *iso*butyl*cyclo*heptane. On oxidation of the hydrocarbon $C_{11}H_{14}$ with potassium permanganate only formic acid (*p*-bromophenacyl ester, m. p. and mixed m. p. 140°) was isolated.[3] Ozonolysis of the hydrocarbon (0·35 g.) in glacial acetic acid (25 c.c.) gave formaldehyde only (dimedone derivative, m. p. and mixed m. p. 190°).

4-iso*Butyl*cyclo*hexanol* (VI).—Phenyl *iso*butyrate was converted by Fries rearrangement into *p-iso*butyrylphenol,[21] which on Clemmensen reduction [22] gave *p-iso*butylphenol, m. p. 50—51°. The latter (10 g.) in ethanol (10 c.c.) was hydrogenated at 110—120°/90 atm. in the presence of "W7" Raney nickel [23] and sodium hydroxide (1 pellet) for 6 hr. The filtered solution was evaporated, and the residue taken up in ether and washed twice with dilute sodium hydroxide solution, then with water. The dried extract was evaporated. The residue of 4-iso*butyl*cyclo*hexanol* distilled at 110—112°/13 mm. (9·3 g.) (Found: C, 76·8; H, 12·9. $C_{10}H_{20}O$ requires C, 76·9; H, 12·8%). The 3:5-*dinitrobenzoate* separated from methanol in plates, m. p. 125—126° (Found: C, 58·4; H, 6·4. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3%).

4-iso*Butyl*cyclo*hexanone* (VII).—The above alcohol (30 g.) in glacial acetic acid (60 c.c.) was added during 30 min. to a stirred solution of chromic acid (14 g.) in water (12 c.c.) and glacial acetic acid (24 c.c.), at <20°. After being kept overnight, the solution was diluted with much water and extracted several times with ether. The combined extracts were washed thoroughly with dilute sodium hydroxide solution and water, dried, and evaporated. The residual 4-iso*butyl*cyclo*hexanone* distilled at 94°/11 mm. (21 g.) (Found: C, 78·0; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). The 2:4-*dinitrophenylhydrazone* separated from ethanol in orange-yellow plates, m. p. 105° (Found: C, 57·75; H, 6·9. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6%).

4-iso*Butyl*cyclo*heptanone* [24] (VIII).—*N*-Nitrosomethylurethane (10·0 g.) was added dropwise to a stirred mixture of 4-*iso*butyl*cyclo*hexanone (11·3 g.), methanol (25 c.c.), and powdered anhydrous potassium carbonate (1·4 g.) during 20 min., at <25° (ice-cooling). After a further 12 hours' stirring the mixture was filtered, the methanol evaporated, water added, and the organic material isolated with ether. Evaporation of the ether gave an oil which distilled at 105—110°/9 mm. (10·6 g.). It was shaken for 24 hr. with saturated sodium hydrogen sulphite

[19] Grignard, *Ann. Chim.* (*France*), 1901, **24**, 433.
[20] Conant and Blatt, *J. Amer. Chem. Soc.*, 1928, **50**, 551.
[21] Cf. Hartung, Munch, Miller, and Crossley, *ibid.*, 1931, **53**, 4149.
[22] Barber and Haslewood, *Biochem. J.*, 1945, **39**, 285.
[23] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.
[24] Cf. Cook, Raphael, and Scott, *J.*, 1951, 695.

solution (200 c.c.). The crystalline bisulphite compound was collected, washed with ether, dried, and shaken with 20% sodium carbonate solution (150 c.c.) and ether (100 c.c.). The ether layer was separated, washed with sodium hydrogen carbonate solution, dried, and evaporated. The residual 4-iso*butyl*cyclo*heptanone* distilled at 106°/10 mm. (5·3 g.) (Found : C, 78·5; H, 12·0. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%). Infrared absorption (liquid film) : CO band at 1704 cm.$^{-1}$, $>CMe_2$ bands at 1363, 1379, and 1169 (not split) cm.$^{-1}$. The *semicarbazone* crystallised from methanol in prisms, m. p. 163° (Found : C, 63·8; H, 10·1. $C_{12}H_{23}ON_3$ requires C, 64·0; H, 10·2%).

4-iso*Butyl*cyclo*heptylamine*.—Anhydrous potassium acetate (7 g.) in hot methanol (30 c.c.) was mixed with hydroxylamine hydrochloride (4·2 g.) in the minimum amount of water. The cooled mixture was filtered, and the filtrate mixed with 4-*iso*butyl*cyclo*heptanone (5 g.), and refluxed on the water-bath for 3 hr. The methanol was evaporated and the residue treated with water and extracted with ether. Evaporation of the dried extract gave 4-iso*butyl*cyclo*heptanone oxime* as a syrup which distilled at 159° (bath)/9 mm. (5·3 g.) (Found : C, 72·3; H, 11·6. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%). The oxime (4·8 g.) in dry ether (40 c.c.) was added dropwise, during 10 min., to a stirred suspension of lithium aluminium hydride (2·5 g.) in dry ether (75 c.c.). The mixture was refluxed on the water-bath for 2 hr., then decomposed with water in the presence of "Celite" (0·5 g.). The ether layer was decanted, dried, and evaporated. The residual 4-iso*butyl*cyclo*heptylamine* distilled at 117—118° (bath)/9 mm. (3·7 g.) (Found : C, 78·0; H, 13·5. $C_{11}H_{23}N$ requires C, 78·1; H, 13·6%).

4-iso*Butyl*-NN-*dimethyl*cyclo*heptylamine* [25] (X).—The foregoing base (1·7 g.) was mixed with 90% formic acid (2·6 g.), with shaking and ice-cooling. Formaldehyde (2·0 g. of 40%) was added, and the mixture heated under reflux on the water-bath for 3 hr. It was then acidified with dilute hydrochloric acid, and neutral matter removed with ether. The aqueous layer was basified with potassium hydroxide, and the basic product isolated with ether. Evaporation of the dried extract gave 4-iso*butyl*-NN-*dimethyl*cyclo*heptylamine*, b. p. 123° (bath)/9—10 mm. (1·5 g.) (Found : C, 79·2; H, 13·8. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7%). Infrared absorption (liquid film) : bands at 1379, 1365, 1153 (not split) cm.$^{-1}$.

The *methiodide*, obtained in warm methanol, crystallised from acetone in needles, m. p. 271° (decomp.) (Found : C, 49·4; H, 8·7. $C_{14}H_{30}NI$ requires C, 49·6; H, 8·8%).

iso*Butyl*cyclo*heptane* (IX).—4-*iso*Butyl*cyclo*heptanone (4 g.), powdered potassium hydroxide (4 g.), diethylene glycol (30 c.c.), and 100% hydrazine hydrate (4 c.c.) were boiled gently under reflux for 1½ hr.[26] The mixture was then distilled until the b. p. of the liquid reached 175—178°, and finally boiled under reflux for a further 3 hr. The cooled mixture was diluted and extracted with ether, and the extract washed with water and dilute hydrochloric acid, dried, and evaporated *via* a Vigreux column. The residual iso*butyl*cyclo*heptane* distilled at 80—81°/13 mm. (Found : C, 85·5; H, 14·0. $C_{11}H_{22}$ requires C, 85·7; H, 14·3%), and had n_D^{25} 1·4490. Infrared absorption (liquid film) : bands at 1364, 1382, and 1168 (not split) cm.$^{-1}$

Permanganate Oxidation of Dioscorine.—The alkaloid (2 g.), potassium hydroxide (5 g.), and water (50 c.c.) were heated on the water-bath for 3 hr. The clear solution was cooled to 0° and kept at this temperature during addition of 4% potassium permanganate solution (250 c.c.) during 30 min., with shaking. The excess of permanganate was destroyed with sulphur dioxide, and the solution acidified with concentrated hydrochloric acid and subjected to continuous ether-extraction for several hours. Evaporation of the ethereal extract gave a semi-crystalline mass of oxalic acid; the crystals (0·05 g.), collected and washed with a little ether, had m. p. about 100°. After drying at 100° the m. p. was 189° (sealed tube), alone or mixed with anhydrous oxalic acid. The bis-*p*-nitrobenzyl ester had m. p. and mixed m. p. 204°.

The acid aqueous solution was rendered alkaline with potassium hydroxide and subjected to further continuous ether extraction. No basic product was obtained. Neutralisation of the aqueous liquid to pH 7, evaporation to dryness, and thorough extraction with methanol also gave nothing save a trace of intractable gum.

Diethyl 3-Bromopropylisobutylmalonate.[27]—Sodium metal (2·4 g.) was powdered and suspended in dry benzene (20 c.c.). Diethyl *iso*butylmalonate [28] (21·6 g.) was added, with shaking and cooling, during 10 min. The mixture was heated for a further 10 min. on the water-bath, by which time all the sodium had disappeared. The cooled solution was added slowly to trimethylene bromide (40·5 g.), with shaking. After refluxing on the water-bath for

[25] Cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[26] Cf. Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[27] Cf. Franke and co-workers, *Sitzungsber. Akad. Wiss. Wien*, 1932, **141**, 881; 1936, **145**, 788.
[28] Fischer and Schmidt, *Ber.*, 1906, **39**, 351.

1 hr., the solution was cooled, treated with water and ether, and the organic layer separated, dried, and evaporated. The residual *bromo-ester* distilled at 160—165°/9—10 mm. (16·3 g.) (Found : C, 50·2; H, 7·5. $C_{14}H_{25}O_4Br$ requires C, 49·9; H, 7·4%). A fore-run, b. p. up to 150°/9—10 mm. (6·8 g.), consisted of unchanged reactants.

Diethyl iso*Butyl*-3-*cyanopropylmalonate*.[27]—The foregoing bromo-ester (16·2 g.), potassium cyanide (15 g.), water (15 c.c.), and ethanol (35 c.c.) were boiled under reflux for 8 hr. The ethanol was distilled off under reduced pressure, and the residue diluted with water. The product was isolated with ether; *diethyl* iso*butyl*-3-*cyanopropylmalonate* distilled at 144—148°/1·5 mm. (11·4 g.) (Found : C, 63·7; H, 8·6. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·8%).

α-iso*Butyladipic Acid*.[27]—The above nitrile (11·4 g.), potassium hydroxide (13 g.), water (26 c.c.), and ethanol (26 c.c.) were boiled under reflux for 10 hr. The alcohol was removed *in vacuo* and the solution diluted, acidified with hydrochloric acid, and extracted with ether. Evaporation of the dried extract gave crystalline α-iso*butyl*-α-*carboxyadipic acid* (9·6 g.), which was heated at 180—190° for 30 min. The liquid product, α-*iso*butyladipic acid, distilled at 205—210° (bath)/0·05 mm. (7·2 g.). The product solidified; it separated from benzene–light petroleum (b. p. 40—60°) in hexagonal prisms, m. p. 60° (Found : C, 59·25; H, 8·5%; equiv., 99·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%; equiv., 101).

β-iso*Butylsuberic Acid*.[28, 20]—α-*iso*Butyladipic acid (11·1 g.) and purified thionyl chloride (20 c.c.) were heated gently on the water-bath for 1 hr. Excess of thionyl chloride was evaporated *in vacuo* and the residual *acid chloride* distilled (b. p. 130—132°/10 mm.; 10 g.) (Found : Cl, 30·0. $C_{10}H_{14}O_2Cl_2$ requires Cl, 29·7%). The acid chloride (10 g.) in dry ether (80 c.c.) was added slowly, with swirling and ice-cooling, during 15 min., to ethereal diazomethane (8·4 g. in 300 c.c.; from 30 g. of nitrosomethylurea). After 12 hr., the ether and excess of diazomethane were removed *in vacuo*. The residual bis-diazoketone (11·0 g.) was dissolved in dioxan (100 c.c.) and added portionwise to a suspension of silver oxide (from 17 g. of silver nitrate) in water (350 c.c.) containing sodium thiosulphate (16·5 g.), with shaking. After being heated at 70—75° for 1½ hr. the solution was cooled and filtered, and the filtrate acidified with nitric acid and extracted with ether. Evaporation of the dried extract gave β-iso*butylsuberic acid*, b. p. 170—172° (bath)/0·05 mm. (7·6 g.) (Found : C, 62·4; H, 9·55%; equiv., 114·1. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%; equiv., 115).

3-iso*Butyl*cyclo*heptanone* (XII).[20]—The foregoing acid (31 g.), iron filings (31 g.), and powdered barium hydroxide (1·7 g.) were heated to 350° during 2 hr., and kept thereat until distillation was complete. The distillate was mixed with ether, and the solution washed with sodium hydrogen carbonate solution and water, dried, and evaporated *via* a Vigreux column. The residual 3-iso*butyl*cyclo*heptanone* distilled at 100°/10—11 mm. (11·7 g.) (Found : C, 78·4; H, 11·8. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%). The *semicarbazone* separated from methanol in rhombic prisms, m. p. 171·5° (Found : C, 64·2; H, 10·0. $C_{12}H_{23}ON_3$ requires C, 64·0; H, 10·2%).

3-iso*Butyl*cyclo*heptylamine*.[21]—The above ketone (5·6 g.), hydroxylamine hydrochloride (5·0 g.), anhydrous potassium acetate (8 g.), methanol (35 c.c.), and water (5 c.c.) were heated on the water-bath for 3½ hr. The methanol was evaporated, the residue diluted with water, and the product isolated with ether. 3-iso*Butyl*cyclo*heptanone oxime* distilled at 150—156° (bath)/9—10 mm. (5·9 g.) (Found : C, 72·2; H, 11·4. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%). The oxime (5·9 g.) in dry ether (30 c.c.) was added slowly, with swirling and cooling, to a suspension of lithium aluminium hydride (2·7 g.) in dry ether (80 c.c.). After refluxing on the water-bath for 20 hr., the mixture was decomposed in the usual manner in the presence of "Celite." The *base* distilled at 121—122° (bath)/9—10 mm. (3·8 g.) (Found : C, 78·0; H, 13·6. $C_{11}H_{23}N$ requires C, 78·1; H, 13·6%).

3-iso*Butyl*-NN-*dimethyl*cyclo*heptylamine* (XI).[25]—The above primary amine (3·0 g.), formic acid (4·6 g. of 90%), and formaldehyde (3·35 g. of 40%) were mixed, with cooling, and heated on the water-bath for 16 hr. The solution was cooled, diluted, and acidified, and neutral matter was removed with ether. The tertiary amine was isolated by basification and ether extraction; 3-iso*butyl*-NN-*dimethyl*cyclo*heptylamine* distilled at 113° (bath)/8 mm. (2·0 g.) (Found : C, 79·1; H, 13·8; *C*-Me, 6·9. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7; 1 *C*-Me, 7·6%). Infrared absorption (liquid film) : bands at 1379, 1362, 1166, and 1152 cm.$^{-1}$. The *methiodide* crystallised from acetone in minute prisms, m. p. 207° (Found : C, 49·8; H, 8·6. $C_{14}H_{30}NI$ requires C, 49·6; H, 8·8%).

[20] "Organic Reactions," Vol. I, p. 51.
[20] Nozoe *et al.*, *Proc. Japan Acad.*, 1950, **26**, (7), 43.
[21] Cf. Walter, *J. Amer. Chem. Soc.*, 1952, **74**, 5185.

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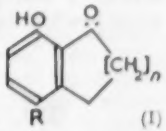
315. peri-*Hydroxy-carbonyl Compounds. Part I. The Synthesis of* peri-*Hydroxy-indanones, -tetralones, and -benzocycloheptenones.*

By N. F. HAYES and R. H. THOMSON.

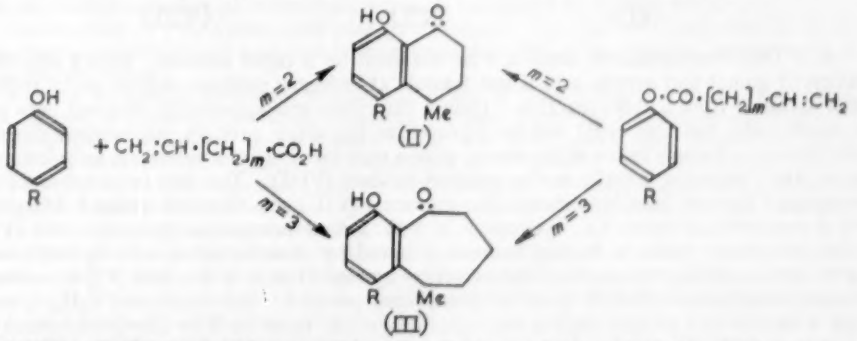
The preparation of compounds of type (I; n = 2, 3, and 4) is described.

IN hydroxy-ketones of type (I), the size of the alicyclic ring will determine the distance between the two oxygen atoms and this in turn will influence the degree of hydrogen bonding. In order to study this effect a number of ketones of type (I) where n = 2, 3, and 4 was required, and the synthetic methods adopted are discussed in this paper. With one exception the ketones were obtained by variations of the Friedel and Crafts procedure, and as the quantities required were small the rapid sodium chloride–aluminium chloride fusion method [1] was used as far as possible.



(I)

Indanones, tetralones, and one benzo*cyclo*heptenone were obtained by Fries rearrangement of aryl esters of appropriate unsaturated acids. This is a recognised method for the preparation of hydroxyindanones, but when it was extended to the synthesis of six- and seven-membered ring ketones we found that the yields fell sharply with increasing ring size. However, alternative syntheses are lengthy and this rapid method is advantageous if only small amounts are needed. The same tetralones and benzo*cyclo*heptenone were also obtained by direct condensation of phenols with unsaturated acids in sodium chloride–aluminium chloride but the yields were very poor, owing, in part, to the volatility of the acids. The examples below illustrate the formation of tetralones by using pent-4-enoic

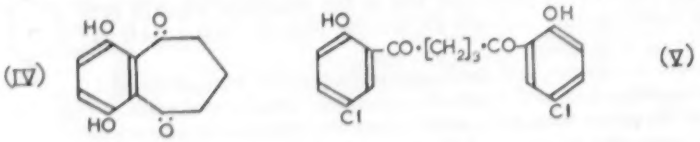


acid, and of the benzo*cyclo*heptenone (III; R = OH) by using hex-5-enoic acid. The structures of the tetralone (II; R = OH) and the benzo*cyclo*heptenone (III; R = OH) were established by conventional methods of synthesis (see Experimental section). The tetralones derived from phenol, *p*-cresol, and *p*-chlorophenol were viscous yellow oils characterised as their 2 : 4-dinitrophenylhydrazones. In view of the low yield of the benzo*cyclo*heptenone (III; R = OH) obtained from quinol, the reaction of hex-5-enoic acid with less reactive phenols was not investigated. The parent benzo*cyclo*heptenone (III; R = OH; H in place of Me) was prepared by standard procedures.

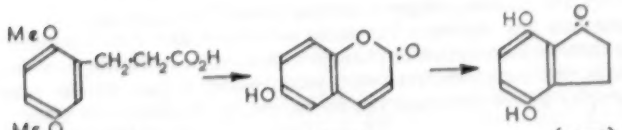
[1] Bruce, Sorrie, and Thomson, *J.*, 1953, 2403.

1 : 5- and 1 : 6-Dihydroxynaphthalene have been reduced to 5- and 6-hydroxytetralone, respectively, by Raney nickel alloy and aqueous sodium hydroxide[2] but we obtained negligible amounts of 8-hydroxy-1-tetralone from 1 : 8-dihydroxynaphthalene by this method. The ketonic material isolated was characterised as its 2 : 4-dinitrophenylhydrazone.

A number of indanones were prepared by reaction of phenols with γ-butyrolactone.[1] Phenol and *p*-cresol afforded two isomers, the 7-hydroxy-derivative predominating in both cases; but only one isomer, 4-chloro-7-hydroxy-3-methylindan-1-one, was isolated on reaction with *p*-chlorophenol, as acylation did not occur *ortho* to the chlorine atom. A parallel was found in the condensation of glutaric anhydride with *p*-chlorophenol; whereas glutaric anhydride and quinol form the cyclic diketone (IV), *p*-chlorophenol under the same conditions yields the bis-condensation product (V). Acylation *ortho* to the chlorine atom in *p*-chlorophenol is known in the condensation with maleic anhydride, which yields 5-chloro-8-hydroxy-1 : 4-naphthaquinone. Two possible explanations were put forward by Baddeley, Makar, and Ivinson[3] and in view of the product we obtained with glutaric anhydride it seems more likely that the cyclisation of the intermediate β-aroylacrylic acid to the quinone depends on its rearrangement to a chelated *cis*-configuration. *p*-Nitrophenol and *p*-hydroxybenzoic acid did not react with γ-butyrolactone when fused in sodium chloride–aluminium chloride at 180°.



(IV) (V)



(VI) (VII) (VIII)

4 : 7-Dihydroxyindanone could not be obtained by a rapid method. Direct condensation of quinol and acrylic acid is not feasible at ordinary pressure and no useful result was obtained from a Fries reaction. Quinol diacrylate was apparently obtained once on a small scale, but this could not be repeated as the crude product polymerised during distillation. A single fusion of the diester gave a very low yield of a yellow phenolic ketone, m. p. 186°, regarded initially as the required product (VIII). This was incorrect and the compound has not been identified. The indanone (VIII) was obtained without difficulty by a conventional route, *i.e.*, cyclisation of β-(2 : 5-dimethoxyphenyl)propionic acid (VI) with phosphoric oxide in boiling benzene followed by demethylation with hydrobromic acid, but an attempt to combine the two steps by rapid fusion of the acid (VI) in sodium chloride–aluminium chloride gave an unexpected product : this compound $C_9H_8O_3$ was not a ketone and yielded only a monoacetate and so must be 3 : 4-dihydro-6-hydroxycoumarin (VII), formed by demethylation and lactonisation of the acid (VI). Dihydrocoumarins are very easily formed by heating β-*o*-hydroxyphenylpropionic acids,[4, 5] and the 6-hydroxy-derivative (VII) was previously obtained by Nebauer and Flatow[6] from a persulphate oxidation of β-*o*-hydroxyphenylpropionic acid and also by reduction of β-(2 : 5-dihydroxyphenyl)acrylic acid with sodium amalgam. Loudon and Razdan[7] have

[2] Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366.
[3] Baddeley, Makar, and Ivinson, *J.*, 1953, 3969.
[4] Ramart-Lucas and Hoch, *Bull. Soc. chim. France*, 1935, **2**, 327.
[5] Jones, Mackenzie, Robertson, and Whalley, *J.*, 1949, 562.
[6] Nebauer and Flatow, *Z. physiol. Chem.*, 1907, **52**, 392.
[7] Loudon and Razdan, *J.*, 1954, 4299.

recently shown that dihydrocoumarins behave like aliphatic lactones when fused for a relatively long time with aluminium chloride, in forming an acyl cation by ring fission, which by an intramolecular cyclisation produces an isomeric hydroxyindanone. We found, in agreement, that prolonged fusion of the dihydrocoumarin (VII) afforded the dihydroxyindanone (VIII).

Experimental

4-(2 : 5-Dimethoxyphenyl)pent-3-enoic Acid.—To methyl β-(2 : 5-dimethoxybenzoyl)-propionate[8] (15 g.), dissolved in ether (90 ml.) and cooled in ice-water, was added, dropwise with swirling, the Grignard reagent from magnesium (2·1 g.) and methyl iodide (12 g.) in ether (40 ml.). The mixture was kept at 0° during the addition and thereafter for 30 min. It was then allowed to warm to 25° for the next 30 min. and finally refluxed on the steam-bath for 3 hr. On cooling, the complex was decomposed with ice (100 g.) and concentrated hydrochloric acid (200 ml.) and boiled for 1 hr. to hydrolyse the ester. The solution was exhaustively extracted with ether, the latter was shaken with aqueous sodium carbonate (3 × 50 ml.), and the combined alkaline extracts were acidified with dilute hydrochloric acid to give 4 g. only of crude acid. Evaporation of the ether extract left an oil (incomplete hydrolysis). Refluxing this with 30% aqueous sodium hydroxide for 1 hr. followed by acidification gave a further 8 g. of crude *acid*, m. p. 96°. It crystallised from water as needles, m. p. 105° (Found: C, 65·9; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

5 : 8-Dihydroxy-4-methyl-1-tetralone.—(*a*) Quinol (1·65 g.) and allylacetic (pent-4-enoic) acid[9] were condensed in a sodium chloride–aluminium chloride melt in the usual way. The product was isolated with chloroform. Evaporation of the solvent, sublimation of the residue at 150°/0·05 mm., and crystallisation from light petroleum (b. p. 100—120°) gave the *tetralone* as yellow needles, m. p. 186° (0·1 g., 3·5%) (Found: C, 68·9; H, 6·0. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%). It gave a green colour with ferric chloride. The *diacetate* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 150° (Found: C, 65·0; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·1; H, 5·8%).

(*b*) Pent-4-enoyl chloride (4 g.) and quinol (2 g.) were refluxed together for 10 min. The resultant ester was distilled at 90—95°/20 mm. and without further purification was added to a melt of anhydrous aluminium chloride (16 g.) and sodium chloride (4 g.) at 180°, and worked up as before. Yellow needles, m. p. 186° (0·3 g., 20%), of the tetralone were obtained.

(*c*) The above pentenoic acid was hydrogenated over Adams catalyst in chloroform–methanol. The resulting pentanoic acid (b. p. *ca.* 100°/0·05 mm.), when fused in aluminium chloride–sodium chloride as before, gave the tetralone, m. p. and mixed m. p. 186° (60%).

Condensation of Pent-4-enoic Acid with Other Phenols.—The methods used were (*a*) direct condensation of phenol and acid, and (*b*) Fries rearrangement of the requisite pent-4-enoate as described previously.[1]

5-Chloro-8-hydroxy-4-methyl-1-tetralone, obtained by both methods from *p*-chlorophenol, was isolated as a viscous yellow oil, which gave a green ferric chloride colour and formed a *2 : 4-dinitrophenylhydrazone*, orange needles, m. p. 256° (from acetic acid) (Found: C, 54·4; H, 4·0; N, 14·9; Cl, 9·0. $C_{17}H_{15}O_6N_4Cl$ requires C, 54·6; H, 3·75; N, 15·0; Cl, 9·5%).

8-Hydroxy-4 : 5-dimethyl-1-tetralone obtained from *p*-cresol as a yellow oil, yielded an orange *2 : 4-dinitrophenylhydrazone*, m. p. 247° (from acetic acid) (Found: C, 58·2; H, 4·85; N, 14·8. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·85; N, 15·1%).

8-Hydroxy-4-methyl-1-tetralone. Phenol and pent-4-enoic acid similarly gave a yellow liquid, which formed a bright red *2 : 4-dinitrophenylhydrazone*, m. p. 220° (from acetic acid) (Found: C, 57·25; H, 4·65; N, 15·9. $C_{17}H_{16}O_5N_4$ requires C, 57·3; H, 4·5; N, 15·8%).

1′ : 4′-Dihydroxy-7-methylbenzocyclohept-1-en-3-one.—(*a*) Hex-5-enoyl chloride[10] (4·5 g.) and quinol (1·5 g.) were refluxed together until evolution of hydrogen chloride had ceased (5—10 min.), and the resultant ester was distilled. Without further purification, this was added to a melt of aluminium chloride–sodium chloride at 180°. The black solid obtained was dried and sublimed at 150°/0·05 mm. to give yellow crystals which were finally purified from light petroleum (b. p. 100—120°) and had m. p. 186° (0·2 g., 5%) (Found: C, 69·6; H, 7·75. $C_{12}H_{14}O_3$ requires C, 69·9; H, 7·75%). Direct condensation of quinol (2 g.) with hex-5-enoic acid (2 g.) in the same medium gave yellow needles, m. p. and mixed m. p. 186° (0·1 g., 2%).

(*b*) Methyl γ-(2 : 5-dimethoxybenzoyl)butyrate (10 g.) was treated with methylmagnesium

[8] Dalal and Nargund, *J. Indian Chem. Soc.*, 1937, **14**, 406.
[9] Conrad and Bischoff, *Annalen*, 1880, **204**, 170.
[10] Helferich and Malkomes, *Ber.*, 1922, **455**, 704

iodide, as in the preparation of the lower homologue; the product was dissolved in methanol and hydrogenated over Adams catalyst. The hexanoic acid (3 g.) was then added to a melt of anhydrous aluminium chloride (20 g.) and sodium chloride (5 g.) at 180° and the ketone sublimed and crystallised from light petroleum (b. p. 100—120°), to give yellow needles, m. p. and mixed m. p. 186° (0·5 g., 20%).

δ-(2 : 5-Dimethoxyphenyl)valeric Acid.—*γ*-(2 : 5-Dimethoxybenzoyl)butyric acid (12 g.) (obtained by the method used by Fieser [11] for the corresponding propionic acid, but not by Shah and Nargund's procedure [12]) was reduced by the Clemmensen–Martin procedure during 24 hr. Distillation *in vacuo* gave a colourless liquid, which solidified. The desired *acid* crystallised from light petroleum (b. p. 50—60°) as prisms, m. p. 50° (6 g., 45%) (Found : C, 65·4; H, 7·3. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·5%).

1′ : 4′-Dihydroxybenzocyclohept-1-en-3-one.—Cyclisation of the dimethoxyphenylvaleric acid in sodium chloride–aluminium chloride yielded the *ketone* as yellow needles, m. p. 121° (from light petroleum, b. p. 100—120°) (30%) (Found : C, 68·6; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%). It gave a transient blue-green colour with ferric chloride. The *diacetate* crystallised from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 112° (Found : C, 65·3; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%), and the 2 : 4-*dinitrophenylhydrazone* formed orange crystals, m. p. 206° (from aqueous acetic acid) (Found : C, 54·8; H, 4·5; N, 14·9. $C_{17}H_{16}O_6N_4$ requires C, 54·8; H, 4·3; N, 15·1%). The *dimethyl ether* (methyl sulphate–acetone–potassium carbonate) separated from light petroleum (b. p. 50—60°) as colourless needles, m. p. 60° (Found : C, 70·8; H, 7·55. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). The ether has since been prepared by Anderson *et al.*[13] by cyclisation of the dimethoxyphenylvaleric acid with phosphoric acid.

8-Hydroxy-1-tetralone.—The procedure adopted was similar to that of Papa *et al.*[9] 1 : 8-Dihydroxynaphthalene (1·4 g.) was dissolved in 10% aqueous sodium hydroxide (100 ml.), the solution warmed to 40—50°, and nickel–aluminium alloy (5 g.) added in portions during 30 min. Then the mixture was refluxed for 1 hr. and filtered into ice and concentrated hydrochloric acid. The product was extracted with ether and distilled *in vacuo*, to give a few drops of a colourless liquid whose 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as red needles, m. p. 253° (Found : C, 56·3; H, 4·15; N, 16·1. $C_{16}H_{14}O_5N_4$ requires C, 56·1; H, 4·1; N, 16·3%). Starting material was recovered together with a small amount of yellow non-ketonic crystals, m. p. 218° (from light petroleum, b. p. 100—120°) (Found : C, 82·8; H, 4·1%).

5-Chloro-8-hydroxy-7-methoxy-1-tetralone.—5-Chloro-7 : 8-dimethoxytetralone (0·5 g.) in glacial acetic acid (5 ml.) and concentrated hydrochloric acid (20 ml.) was refluxed for 2 hr. After cooling and dilution with water (50 ml.), the precipitate was collected, washed, dried, and crystallised from light petroleum (b. p. 80—90°) as yellow needles, m. p. 104° (0·3 g., 60%). Ghosh and Robinson [14] obtained this compound as a by-product in the cyclisation of *γ*-(2-chloro-4 : 5-dimethoxyphenyl)butyric acid. The *acetate* separated from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 97° (Found : C, 57·9; H, 4·8; Cl, 13·6. $C_{13}H_{13}O_4Cl$ requires C, 58·1; H, 4·8; Cl, 13·2%).

Condensation of γ-Butyrolactone with Various Phenols.—The general procedure of Bruce, Sorrie, and Thomson [1] was used.

(*a*) *p*-Cresol and *γ*-butyrolactone yielded two products. The major portion, 7-*hydroxy*-3 : 4-*dimethylindan*-1-*one* (57%), was obtained as colourless prisms, m. p. 54° (from light petroleum b. p. 50—60°). This compound was only slightly soluble in aqueous sodium hydroxide and gave an intense violet ferric chloride colour. The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as orange needles, m. p. 262° (Found : C, 57·1; H, 4·5; N, 15·9. $C_{17}H_{16}O_5N_4$ requires C, 57·3; H, 4·5; N, 15·7%). The second product was obtained as a sublimate after distillation of the more volatile isomer. On crystallisation from water 4-*hydroxy*-3 : 7-*dimethylindan*-1-*one* formed colourless needles, m. p. 175° (4%) (Found : C, 74·8; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). This indanone was readily soluble in cold aqueous sodium hydroxide but gave no colour with ferric chloride. The 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene as dark red needles, m. p. 300° (Found : C, 57·05; H, 4·5; N, 15·3%).

(*b*) Phenol and *γ*-butyrolactone similarly gave two isomeric indanones. 7-Hydroxy-3-methylindanone distilled as a colourless liquid, b. p. 63°/0·05 mm. (50%) (Found : C, 74·05;

[11] Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2966.
[12] Shah and Nargund, *J. Univ. Bombay*, 1947, **15**, *A*, 19.
[13] Anderson, Horton, Walker, and Weiler, *J. Amer. Chem. Soc.*, 1955, **77**, 598.
[14] Ghosh and Robinson, *J.*, 1944, 506.

H, 6·3. Calc. for $C_{10}H_{10}O_3$: C, 74·1; H, 6·2%). The *acetate* separated from aqueous acetic acid as colourless needles, m. p. 120° (Found: C, 70·7; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%), and the 2 : 4-*dinitrophenylhydrazone* from acetic acid as orange-red needles, m. p. 256° (Found: C, 57·45; H, 4·05; N, 16·7. $C_{16}H_{14}O_6N_4$ requires C, 57·8; H, 4·2; N, 16·9%). The isomeric ketone, 5-hydroxy-3-methylindanone, formed colourless needles (from water), m. p. 148° (8%) (Found: C, 73·75; H, 6·2%). Its 2 : 4-*dinitrophenylhydrazone* separated from nitrobenzene as red crystals, m. p. 270° (Found: C, 57·75; H, 4·5; N, 16·8%).

(*c*) *p*-Chlorophenol and γ-butyrolactone formed only one product, 4-*chloro*-7-*hydroxy*-3-methylindanone, which crystallised from aqueous alcohol in colourless needles, m. p. 54° (50%) (Found: C, 60·6; H, 4·7; Cl, 17·9. $C_{10}H_9O_2Cl$ requires C, 60·7; H, 4·55; Cl, 18·5%). The *acetate* formed colourless needles, m. p. 118° (from aqueous acetic acid) (Found: C, 60·35; H, 4·25; Cl, 14·9. $C_{12}H_{11}O_3Cl$ requires C, 60·1; H, 4·5; Cl, 15·2%), and the 2 : 4-*dinitrophenylhydrazone* also crystallised from aqueous acetic acid forming orange needles, m. p. 248° (Found: C, 51·1; H, 3·5; N, 14·9; Cl, 9·5. $C_{16}H_{13}O_6N_4Cl$ requires C, 50·9; H, 3·45; N, 14·8; Cl, 9·7%).

7-*Hydroxy*-4-*methylindan*-1-*one*.—*p*-Cresol (1 g.) and acryloyl chloride (1 g.) were refluxed until hydrogen chloride was no longer evolved (5 min.) and the resultant ester distilled (b. p. *ca.* 200°). This liquid (0·7 g.) was added to a melt of anhydrous aluminium (20 g.) and sodium chloride (5 g.) at 180° and after 2 min. at this temperature the mixture was cooled and decomposed with ice and hydrochloric acid. The ketone was purified by sublimation at 60°/0·05 mm. and crystallisation from aqueous alcohol, forming colourless needles, m. p. 110° (0·4 g., 26%). 7-Hydroxyindan-1-one, m. p. 111°, and 4-chloro-7-hydroxyindan-1-one, m. p. 122°, were similarly obtained from phenol and *p*-chlorophenol respectively.

Quinol Diacrylate.—Acryloyl chloride (1·5 g.) and quinol (0·9 g.) were refluxed together for 5 min. The solid deposited on cooling crystallised from aqueous alcohol, to give the *diester* as colourless plates, m. p. 88° (Found: C, 66·0; H, 4·6. $C_{16}H_{16}O_4$ requires C, 66·0; H, 4·6%). Attempts to repeat this experiment failed.

1 : 3-*Di*-(2-*hydroxy*-5-*chlorobenzoyl*)*propane*.—*p*-Chlorophenol (5·7 g.) and glutaric anhydride (5 g.), fused in sodium chloride–aluminium chloride, gave the *diketone* as pale yellow needles (from aqueous alcohol), m. p. 156° (5·8 g.) (Found: C, 57·5; H, 3·8; Cl, 20·5. $C_{17}H_{14}O_4Cl_2$ requires C, 57·8; H, 4·0; Cl, 20·1%). The *bis*-2 : 4-*dinitrophenylhydrazone* separated from *o*-dichlorobenzene as orange crystals, m. p. 258° (Found: C, 48·7; H, 3·2; N, 15·5; Cl, 10·4. $C_{29}H_{22}O_{10}N_8Cl_2$ requires C, 48·8; H, 3·1; N, 15·7; Cl, 10·0%), and the *diacetate* separated from light petroleum (b. p. 100—120°) as colourless rosettes, m. p. 92° (Found: C, 57·4; H, 4·3; Cl, 15·95. $C_{21}H_{18}O_6Cl_2$ requires C, 57·7; H, 4·1; Cl, 16·2%).

3 : 4-*Dihydro*-6-*hydroxycoumarin*.—To a molten mixture of anhydrous aluminium chloride (30 g.) and sodium chloride (7·5 g.) at 180°, was added slowly with stirring, β-(2 : 5-dimethoxyphenyl)propionic acid[8] (2 g.). After 5 min., the mixture was cooled, treated with water (200 ml.) and concentrated hydrochloric acid (100 ml.), and extracted with ether. After being dried ($MgSO_4$), the solvent was removed and the residue, crystallised from water, had m. p. 163° (55%) (Found: C, 65·0; H, 5·1. Calc. for $C_9H_8O_3$: C, 65·2; H, 4·9%). It gave no ferric chloride colour and formed an acetate, m. p. 86°.

4 : 7-*Dihydroxyindan*-1-*one*.*—(*a*) 4 : 7-Dimethoxyindan-1-one[15] (0·2 g.) was dissolved in 48% hydrobromic acid (10 ml.) and refluxed for 2 hr. The solvent was removed *in vacuo* and the residue crystallised from ethyl acetate–light petroleum (b. p. 100—120°) to give colourless needles, m. p. 198° (Found: C, 65·75; H, 4·75. $C_9H_8O_3$ requires C, 65·85; H, 4·9%).

(*b*) 3 : 4-Dihydro-6-hydroxycoumarin (0·1 g.) was added to a melt of anhydrous aluminium chloride (10 g.) and sodium chloride (2·5 g.) at 180° and the temperature was maintained between 180° and 220° for 45 min. After decomposition of the complex in the usual way, ether-extraction yielded a colourless solid, which crystallised from ethyl acetate–light petroleum in needles, m. p. and mixed m. p. 198°.

One of us (N. F. H.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance.

The University, Old Aberdeen, Scotland. [*Received, December 7th*, 1955.]

* The compound named 4 : 7-dihydroxyindanone in ref. 7, p. 4302, should be 5 : 7-dihydroxyindanone.

[15] Arnold and Zaugg, *J. Amer. Chem. Soc.*, 1941, **63**, 1317.

316. *The Influence of the Reaction Medium on the Relative Apparent Electron-donating Effects of Different Alkyl Groups.*

By E. Spinner.

This study of the rates of ionisation of the halides $R{\cdot}CMe_2Cl$ (R = Me, Et, Pr^i, Bu^t) in five widely differing solvents was undertaken to elucidate further the nature of the Baker–Nathan effect which is variously attributed to hyperconjugation and to steric resistance to bond contraction. The former theory is shown to demand that the effect, being of a polar nature, be most pronounced in the best cation-solvating solvents, while the latter theory demands the reverse. Actually, the relative rates of ionisation vary greatly from solvent to solvent, and the data, though somewhat irregular, are much more readily reconciled with the latter view.

Alkyl groups may stabilise electron-deficient molecules by two different mechanisms; one type of stabilisation, increasing from Me to Bu^t, is due to the inductive effect of alkyl groups; the other type, increasing in the order $H < Bu^t < Pr^i < Et < Me$ and known as the Baker–Nathan effect, is the subject of controversy. Baker and Nathan [1] ascribed it to a mesomeric or electromeric electron release by alkyl groups (hyperconjugation) which is possible if at least one hydrogen atom is linked to a carbon atom attached to an unsaturated centre and which increases in importance with the number of hydrogen atoms so linked; structures like $H^+CH_2{\cdot}CH{\cdot}\bar{C}H_2$ in the case of propene are considered to contribute.

Burawoy and Spinner,[2] on the other hand, have criticised the theory of hyperconjugation and ascribed the Baker–Nathan effect to steric resistance to bond contraction. When an atom acquires a (partial) positive charge its bond radius contracts and the linkages attached to it become stronger with a consequent stabilisation of the molecule.[3] Such stabilisations will be referred to as contraction stabilisations. The contraction stabilisation incurred when the atom to which an alkyl group is attached acquires a (partial) positive charge decreases with the size of the group, *i.e.*, in the order $Me > Et > Pr^i > Bu^t \gg H$*), owing to intramolecular steric repulsions.

One important difference between these two theories lies in the fact that hyperconjugation effects, like all mesomeric and electromeric effects, are true polar effects, *i.e.*, stabilisation is due to the transfer of electronic charge from the alkyl group to the electron-deficient centre. The contraction effect, on the other hand, is not a polar effect, contraction stabilisation being due essentially to increased orbital overlap giving rise to stronger σ-bonds. (This effect must not be confused with the bond shortening due to increased double-bond character which is demanded by the theory of hyperconjugation and inseparable from the electron-donating effect.) The total stabilisation of an electron-deficient entity by an alkyl group, due to the *sum* of the inductive + hyperconjugation *or* contraction effects, which will be called the apparent electron-donating effect of the alkyl group, is influenced by the reaction medium. It will be shown by a complete analysis of the energetics of a typical heterolytic reaction, *viz.*, the dissociation $R{\cdot}CMe_2Cl \longrightarrow R{\cdot}\overset{+}{C}Me_2 + \bar{Cl}$ (studied in the present work), that the two theories lead to opposite predictions concerning the relative prominence of the Baker–Nathan effect in different media.

* The contraction of the C–H bond would be resisted by very formidable *internuclear* repulsions.

[1] Baker and Nathan, *J.*, 1935, 1844.
[2] Burawoy and Spinner, *J.*, 1954, 3752.
[3] Burawoy, "Contribution à l'Étude de la Structure Moléculaire," Desoer, Liège, 1948, p. 73; *Trans. Faraday Soc.*, 1944, **40**, 537; *Chem. and Ind.*, 1944, **63**, 434.

For energetic purposes the reaction may be considered to proceed by the following stages:

$$R{\cdot}CMe_2Cl \longrightarrow R{\cdot}\dot{C}Me_2 + \dot{Cl} \longrightarrow \underset{\text{Unrearranged}}{R{\cdot}\overset{+}{C}Me_2} + \bar{Cl} \longrightarrow \underset{\text{Rearranged}}{R{\cdot}\overset{+}{C}Me_2} + \bar{Cl}$$

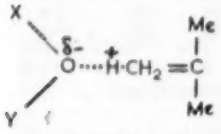
(I) (II) (III)

[The relative positions of the atoms in $R{\cdot}CMe_2$ are considered to remain unchanged during stages (I) and (II).]

The (electronic) potential energy difference between the initial and the transition state consists of: (1) the energy of heterolytic fission of the C–Cl bond; (2) the ionisation potential of $R{\cdot}\dot{C}Me_2$ and the electron affinity of $\dot{Cl}$, the latter being independent of R; (3) the energy of rearrangement of the ion $R{\cdot}\overset{+}{C}Me_2$; (4) the difference between the energies of solvation of $R{\cdot}CMe_2Cl$ on the one hand and of $R{\cdot}\overset{+}{C}Me_2$ and $\bar{Cl}$ on the other; (5) the difference in intramolecular van der Waals–London cohesion energy * between $R{\cdot}CMe_2Cl$ and $R{\cdot}\overset{+}{C}Me_2 + \bar{Cl}$.

Factor (1) is almost independent of the polar effect of R but is affected by its size; if R is bulky, dissociation relieves intramolecular steric strain.[5] The ionisation potential of $R{\cdot}CMe_2$ (2) is determined by the polar effects of R, *i.e.*, by its ability to transfer electronic charge to C^+. Such a transfer will be strongly facilitated by the vicinity near R of the negative pole(s) of polar (or polarised) molecules. Factor (3) is composed of the relief in intramolecular steric strain obtained when the ion becomes planar [6] and the contraction stabilisations in the ion; both will be almost unaffected by the nature of the solvent.

The energy of solvation of $R{\cdot}\overset{+}{C}Me_2$ (4) is determined to some extent, but by no means wholly, by the ease with which the negative poles of the solvent molecules can approach C^+; this will be reduced if R is bulky,[6,5] the reduction being greatest in the solvents which solvate the cation most effectively. However, the transition state obtained in ionisation



(IV)

Assistance of hyperconjugation by a solvent molecule, which increases with the electron availability on O, illustrated for the $[Me_3C]^+$ ion.

reactions consists of a pair of *partially* solvated ions;[7] the access of solvent molecules to C^+ is restricted in any case; the attractions between solvent and R itself (which is accessible) cannot be ignored. The intramolecular van der Waals–London attractive forces (5) stabilise the undissociated halide, stabilisation increasing with the number of atoms in R. However, these forces (which will be discussed fully in another publication) tend to be relatively less important in saturated systems; they will only be affected slightly by the solvent.

In most heterolytic reactions stabilisations due to polar effects (polar stabilisations) are decisive and factor (2) overshadows all others. Hyperconjugation transfers electronic charge more effectively than does the inductive effect and is the potentially stronger polar effect; Shiner [8] has already pointed out that it should be favoured by solvents which are good acceptors in hydrogen-bond formation (see IV). Kloosterziel and Backer [9] found that the (negative) Hammett's σ-value for the Me group is highest in the most polar solvent, but this can be due to enhancement of either the inductive or the hyperconjugation effect.

* This type of molecular energy was first considered by Eyring.[4]

[4] Eyring, *J. Amer. Chem. Soc.*, 1932, **54**, 3191.
[5] Brown and Fletcher, *ibid.*, 1949, **71**, 1845; Brown and Stern, *ibid.*, 1950, **72**, 5068.
[6] Shorter and Hinshelwood, *J.*, 1949, 2412.
[7] Cf., *e.g.*, Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 312.
[8] Shiner, *J. Amer. Chem. Soc.*, 1953, **75**, 2925; 1954, **76**, 1603.
[9] Kloosterziel and Backer, *ibid.*, 1952, **74**, 5806.

(The reaction studied, *viz.*, the addition of a proton to *p*-toluidine, is closely comparable to the ionisation of an alkyl halide. It is noteworthy that the σ-value of Me is highest in the most polar medium, although the better solvation of the N^+ atom could conceivably reduce the electron demand on the Me group.)

Since the Baker–Nathan effect is not observed in electronic absorption spectra, Burawoy and Spinner [10] conclude that it is not a polar effect, but related to factor (3). Energies of electronic excitation are composed of factors of the type of (2), (4), and (5), but not (1) or (3), and in some of the systems studied the polar stabilisation of the excited state by alkyl groups is very great. Sweeney and Schubert,[11] on the basis of the same evidence, also concluded that the Baker–Nathan effect cannot be a polar effect; confining their attention to cations (in general), they ascribe it to steric inhibition of solvation of the ion, *i.e.*, they regard it as related to factor (4) (this view has been criticised by Burawoy and Spinner [10]). To summarise, if the Baker–Nathan effect is a polar effect, *i.e.*, is due to hyperconjugation, *or* if it is due to steric inhibition of solvation, it should be most pronounced in solvents which solvate cations most effectively; if it is due to neither of these causes, these will be just the solvents in which the inductive effect is most prominent.

Little previous work on the variation with solvent of the apparent electron-donating effects of alkyl groups has been carried out. Hughes, Ingold, and Taher [12] found the Baker–Nathan effect in the solvolysis rates of the *p*-alkyldiphenylmethyl chlorides to be more prominent in 80% aqueous acetone than in pure ethanol. Berliner, Beckett, Blomers, and Newman [13] observed a pure Baker–Nathan order in the rates of alkaline hydrolysis of the ethyl *p*-alkylbenzoates in 85% aqueous ethanol, but a pure inductive order for the same reaction when carried out in 56% aqueous acetone (in which solvent the σ-value for Me itself is higher). The significance of these data (collected in Table 1) was difficult to assess. Ethanol and 80% aqueous acetone are solvents of similar ionising power; 56% aqueous acetone is a more highly polar medium than 85% aqueous ethanol.

TABLE 1. *Velocity constants in different solvents.*

Reaction		Medium	H	Me	Et	Pr^i	Bu^t
p-$C_6H_4R{\cdot}CHPhCl$ = p-$C_6H_4R{\cdot}CHPh^+ + Cl^-$	(*a*)	80% $COMe_2$	7·28	156	126	101	79·6
		EtOH	5·30	124	120	106	98·7
p-$C_6H_4R{\cdot}CO_2Et + OH^-$ = p-$C_6H_4R{\cdot}CO_2^- + EtOH$	(*b*)	56% $COMe_2$	2·89	1·18	1·06	0·964	0·908
		85% EtOH	0·614	0·273	0·293	0·314	0·342

(*a*) Values of 10^5k_1 (sec.$^{-1}$) at 25°. (*b*) Values of 10^5k_2 (l. mole^{-1} sec.$^{-1}$) at 25°.

In the present work the rates of ionisation of the series of halides $R{\cdot}CMe_2Cl$ (R = Me, Et, Pr^i, Bu^t) were studied in a number of solvents varying widely in polar properties. The results are collected in Table 2. Such halides undergo solvolysis by a unimolecular mechanism (ionisation) even in solvents of low polarity.[14] *iso*Propyl chloride (R = H) was not studied because the mechanism of solvolysis is uncertain in many solvents. The complete series of halides has been examined in 80% aqueous ethanol by Shorter and Hinshelwood [6] and by Brown *et al.*[5] Their results are included in Table 2.

The solvolyses in 70% aqueous methanol, 90% aqueous propan-1-ol, and 90% aqueous acetone are free from kinetic complications. In the case of the hydrolyses in 94% formic acid, which contained 1% of water, a slight excess of calcium formate over alkyl halide, and 5% of acetone (the presence of which is essential to ensure speedy dissolution of the higher halides at the commencement of reaction), the first-order velocity coefficients decrease as the reaction proceeds, presumably owing to reversibility of heterolysis (see Table 5); the values of the "constants" given in Table 2, being average values, are of little absolute significance, but they represent the relative reactivitites of the halides quite accurately. Measurement of the rate of hydrogen chloride generation in absolute propanol is complicated by the fact that there is appreciable reaction between hydrogen chloride and solvent at 35°; the allowance made for this is rather approximate. The accuracy

[10] Burawoy and Spinner, *J.*, 1955, 2085.
[11] Sweeney and Schubert, *J. Amer. Chem. Soc.*, 1954, **76**, 4625.
[12] Hughes, Ingold, and Taher, *J.*, 1940, 949.
[13] Berliner, Beckett, Blommers, and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 4940.
[14] Hughes, *J.*, 1935, 255; Cooper and Hughes, *J.*, 1937, 1183.

TABLE 2. *Velocity constants for the reaction* $R{\cdot}CMe_2Cl \longrightarrow R{\cdot}CMe_2^+ + Cl^-$ *in different solvents.*[a]

Solvent	Temp.	R =	Me	Et	Pr^i	Bu^t
94% $H{\cdot}CO_2H$	15°	k_1 (1)	1·08	1·98	1·44	2·62
		(2)	1·02	1·74	1·32	2·40
		mean	1·05	1·86	1·38	2·46
		$k_{rel.}$	1·0	1·8	1·3	2·3
70% MeOH	35	k_1 (1)	0·830	1·65	1·13	1·88
		(2)	0·852	1·62	1·12	1·82
		mean	0·841	1·64	1·12	1·85
		$k_{rel.}$	1·00	1·95	1·33	2·20
80% EtOH	25 [b]	$10^5 k_1$	3·3	5·5	2·9	4·0
		$k_{rel.}$	1·00	1·66	0·88	1·21
	35 [c]	$10^5 k_1$	4·07	6·55	3·49	4·52
		$k_{rel.}$	1·00	1·61	0·86	1·11
90% Pr^{n}OH	35	$10^5 k_1$ (1)	1·84	2·90	1·51	1·92
		(2)	1·87	2·91	1·54	1·92
		mean	1·86	2·91	1·53	1·92
		$k_{rel.}$	1·00	1·56	0·82	1·03
90% $COMe_2$	35	$10^5 k_1$ (1)	1·43	2·20	1·46	2·76
		(2)	1·46	2·21	1·47	2·79
		mean	1·45	2·21	1·47	2·78
		$k_{rel.}$	1·00	1·52	1·01	1·92
100% Pr^{n}OH	35	$10^5 k_1$ (1)	0·78	1·40	0·91	1·31
		(2)	0·82	1·45	0·92	1·33
		mean	0·80	1·43	0·92	1·32
		$k_{rel.}$	1·00	1·8	1·15	1·65

(*a*) For composition of solvents see Experimental section.
(*b*) Brown and Fletcher; Brown and Stern.[5]
(*c*) Shorter and Hinshelwood.[6]

of the absolute velocity constants obtained in this solvent is uncertain, but the relative rates are fairly accurate.

The order in which the various alkyl groups facilitate the ionisation of $R{\cdot}CMe_2Cl$ varies considerably from solvent to solvent; in formic acid and 70% aqueous methanol the inductive effect is preponderant, while in 90% aqueous propanol the inductive and the Baker–Nathan effect are about equally strong. There is, however, not complete regularity as between solvents; the ion-solvating powers decrease from 70% aqueous methanol to 80% aqueous ethanol to 90% aqueous propanol to 100% propanol, but these solvents do not form a continuous sequence. In Table 3 the solvents are listed in the order in which they enhance the activating effects of the various alkyl groups relative to methyl, and it is seen that for all groups the order is 70% MeOH $\gg$ 94% $H{\cdot}CO_2H$ > 80% EtOH > 90% PrOH; these solvents may be regarded as "normal." The positions of 90% aqueous acetone and propanol in the lists are, however, not fixed, and these two solvents, especially the latter, must be regarded as anomalous.

In Table 3 the solvents are also compared as regards their effects on absolute rates of ionisation, *i.e.*, their ionising power, and as regards the electrical conductivities which hydrogen chloride exhibits in them. All the lists are headed by the most polar solvents, but there is no strict parallelism between any of the properties listed.

The ionising power of a solvent depends on its ability to solvate both anion and cation (and solvation of the small anion is likely to be more important). The dimensions of the transition state, especially the C–Hal distance, will also be determined by the ionising power of the solvent, and since this factor could conceivably be of some importance there might be a parallelism between the solvent effects on absolute ionisation rates and the enhancement by the solvent of the activating effect of alkyl groups. Actually, there is no close parallelism, and this factor seems to be overshadowed (at least in the case of the "normal" solvents). As shown above, the apparent electron-donating effect of alkyl groups should depend on the ability of the solvent to solvate the cation. The electrical conductivities of the hydrogen chloride solutions depend on the basicities and ionising powers of the media, and on the mobility of the ions (*i.e.*, the weight and size of the solvent molecules); basicity and cation-solvating power are closely related properties depending on the electron availability at the negative pole of the molecule.

90% Aqueous acetone, which might be expected to be similar to 90% aqueous propanol, is more " polar " than expected as regards both its conducting power and its ability to enhance the apparent electron-donating effect of alkyl groups (especially of Bu^t). This

TABLE 3. *Relative reactivities and absolute ionisation rates of* $R{\cdot}CMe_2Cl$, *and the electrical conductivity of* HCl *solutions: order of solvents.*

Et/Me Rate ratio	70% MeOH > 1·95	Pr^{n}OH > 1·8	$H{\cdot}CO_2H$ > 1·8	80% EtOH > 1·61	90% Pr^{n}OH > 1·56	90% $COMe_2$ 1·52
Pr^i/Me Rate ratio	70% MeOH > 1·33	$H{\cdot}CO_2H$ > 1·3	Pr^{n}OH > 1·15	90% $COMe_2$ > 1·01	80% EtOH > 0·86	90% Pr^{n}OH 0·82
Bu^t/Me Rate ratio	70% MeOH ≈ 2·20	$H{\cdot}CO_2H$ > 2·3	90% $COMe_2$ > 1·92	Pr^{n}OH > 1·65	80% EtOH > 1·11	90% Pr^{n}OH 1·03
Absolute k_1 at 35° (a)	$H{\cdot}CO_2H$ ~20 (b)	> 70% MeOH > 1	80% EtOH > 5×10^{-2}	90% Pr^{n}OH > 2×10^{-2}	90% $COMe_2$ > 2×10^{-3}	Pr^{n}OH 10^{-3}
$10^4 \times$ Spec. cond. of $N/200$-HCl in solvent at 35°	70% MeOH > 7·2	$H{\cdot}CO_2H$ (c) ≈ 4·2	80% EtOH > 4·1	90% $COMe_2$ > 3·1	90% Pr^{n}OH > 1·9	Pr^{n}OH 1·3

The rate ratios in the solvent 94% $H{\cdot}CO_2H$ given here were determined at 15°; they must be lowered slightly to be comparable with the other rate ratios, determined at 35°.

(*a*) Approx. average for all chlorides. (*b*) Estimated.
(*c*) Estimated; the conductivity of $N/200$-HCl in pure $H{\cdot}CO_2H$ at 25° is 0·00035,[18] that of 80% EtOH at 25° is 0·00034.

is undoubtedly due to the structure of the acetone molecule: the negative end of the dipole, the oxygen atom, is readily accessible, while the positive end, the carbonyl-carbon atom, is inaccessible. As a result, acetone molecules should solvate anions very poorly but cations very effectively; the cation-solvating power of acetone will be further enhanced by the high polarisibility of the carbonyl group in the direction towards the oxygen atom. In view of Burawoy's arguments[3] against the concept of the delocalisation of electrons, the author regards this polarisibility as wholly inductomeric in nature, but according to conventional views the carbonyl group can also be regarded as possessing a high electromeric polarisibility towards oxygen.

Propan-1-ol, the least polar of the solvents examined, has the lowest ionising and conducting powers, but it does not occupy an extreme position as regards its ability to enhance the apparent electron-donating effects of alkyl groups. For some reason the higher alkyl halides ionise more readily in this solvent than might be expected. In water-free solvents of very low polarity the solvation of the cation is probably due largely to van der Waals–London as well as electrostatic attractive forces. In addition, the nature of the transition state is likely to be somewhat different in these solvents.

As regards the " normal " solvents, the position is clear. The order in which these solvents favour the inductive effect at the expense of the Baker–Nathan effect is 70% MeOH ≈ 94% $H{\cdot}CO_2H$ > 80% EtOH > 90% Pr^{n}OH; *i.e.*, the inductive order becomes more prominent as the cation-solvating power of the solvent increases. This supports the idea that the Baker–Nathan effect is neither a polar effect, *i.e.*, not due to hyperconjugation, nor the consequence of steric inhibition of cation solvation (which is completely over-shadowed by other effects; the greater the intramolecular transfer of electronic charge to the C^+ atom, the less will be the importance of solvation of that atom). The results are in agreement with the view that the Baker–Nathan effect is due to steric resistance to bond contraction, and that the only *true* polar effects exerted by alkyl groups are of the inductive and inductomeric type.

EXPERIMENTAL

Materials.—Liquid alkyl halides were purified by alternate fractional distillation and fractional freezing; *tert.*-butyl chloride had b. p. 49·5°/736 mm., m. p. −23°; 1 : 1-dimethylpropyl chloride had b. p. 85°/750 mm., m. p. −73°; 1 : 1 : 2-trimethylpropyl chloride had b. p.

[18] Schlesinger and Martin, *J. Amer. Chem. Soc.*, 1914, **36**, 1589.

110°/770 mm., m. p. −11°. 1 : 1 : 2 : 2-Tetramethylpropyl chloride [16] was purified by recrystallisation from absolute methanol and sublimation *in vacuo* to give transparent plates of m. p. 129° (in a sealed capillary tube).

Solvents.—70% Aqueous methanol : 600 ml. of water made up to 2 l. (at room temp., *ca* 17·5°) with pure lime-dried methanol. 90% Aqueous propan-1-ol and 90% aqueous acetone : 200 ml. of water made up to 2 l. (at room temperature) with pure lime-dried propanol and pure Anhydrone-dried acetone, respectively. 100% Propanol was lime-dried. 94% Formic acid : see below.

Rate Determinations in Solvents Other than 94% *Formic Acid.*—Normally, 0·7—0·9 g. of alkyl halide at 35° was dissolved in 100 ml. of solvent at 35°. In the case of 1 : 1 : 2 : 2-tetramethylpropyl chloride in 70% aqueous methanol, direct dissolution being too slow, the halide was dissolved quickly in 36·6 ml. of pure methanol and a mixture of 15 ml. of water and 50 ml. of aqueous methanol at 35° was added rapidly and with stirring, giving a final solvent composition identical with that of 70% aqueous methanol. In all other instances the same sample of solvent was used for all halides.

The rate of hydrogen chloride generation was followed conductometrically; the cell was fitted with platinised-platinum electrodes and a mechanical stirrer, and the cell constant was checked before and after each determination. Charts showing conductivity against hydrogen chloride concentration were prepared for each solvent used. The conductivities of hydrogen chloride solutions in absolute propanol decrease with time, quite rapidly at first, more slowly later (after some water has been formed); the conductivities used in the chart were those obtained after time intervals comparable with those encountered in rate determinations.

The reactions in 70% aqueous methanol were followed to completion, equilibrium corresponding to about 99% of solvolysis. In the other solvents reactions were pursued up to 10—15% of solvolysis; the velocity coefficients calculated are those for first-order irreversible reactions. In all cases total halide contents (ionised + labile organic) were estimated by titration of samples of the reaction mixture by Volhard's method. Data for one typical solvolysis in each solvent are shown in Table 4. The reaction between hydrogen chloride and absolute propanol is responsible for the observed gradual decrease in the velocity coefficient in this solvent.

TABLE 4. *Solvolyses at* 35°.*

CMe_2Pr^iCl in 70% aq. MeOH : a = 69·8			CMe_2EtCl in 90% aq. $COMe_2$: a = 70·9			CMe_2Bu^tCl in 90% aq. Pr^nOH : a = 67·5			CMe_2Cl in Pr^nOH : a = 54·3		
t (min.)	x	10^2k	t (hr.)	x	10^2k	t (hr.)	x	10^2k	t (hr.)	x	10^4k
5	6·1	1·83	2	0·31	2·19	0·5	0·63	1·88	16	0·7	8·1
10	11·9	1·87	4	0·63	2·23	1·0	1·28	1·91	20	0·85	7·9
15	17·1	1·87	6	0·94	2·22	1·5	1·90	1·92	24	1·02	8·0
20	21·75	1·87	8	1·24	2·19	2·0	2·55	1·93	40	1·68	7·8
25	26·0	1·86	10	1·53	2·19	2·5	3·17	1·93	44	1·82	7·7
30	29·7	1·85	25	3·77	2·18	3·0	3·76	1·91	48	2·0	7·8
35	33·5	1·87	27·5	4·14	2·19	3·5	4·36	1·91	64	2·63	7·8
40	36·75	1·87	30	4·52	2·20	4·0	4·96	1·91	68	2·77	7·7
45	39·75	1·87	32	4·80	2·19	4·5	5·57	1·91	72	2·93	7·7
50	42·5	1·88	47·5	7·13	2·23	5·0	6·16	1·91	88	3·50	7·6
55	44·9	1·87	50	7·48	2·23	5·5	6·76	1·91		Mean	7·8
60	47·2	1·88	52·5	7·82	2·23	6·0	7·37	1·93			
70	51·1	1·88	55	8·17	2·22	6·5	7·98	1·94			
80	54·3	1·88		Mean	2·21	7·0	8·53	1·93			
90	57·0	1·89				7·5	9·07	1·93			
100	59·2	1·90				8·0	9·65	1·93			
110	60·9	1·90					Mean	1·92			
120	62·4	1·91									
∞	69·2	—									
	Mean	1·88									

* a and x denote the initial concentration of alkyl halide and the concentration of hydrogen chloride after time t (in ml. of N/10), respectively.

Rate Determinations in 94% *Formic Acid.*—These were carried out by a modification of the method of Bateman and Hughes.[17] A solution of calcium formate (0·32 g.) and water (0·5 ml.)

[16] Calingaert, Soroos, Hnidza, and Shapiro, *ibid.*, 1944, **66**, 1389.
[17] Bateman and Hughes, *J.*, 1937, 1187; 1940, 935.

TABLE 5. *Hydrolysis of* CMe_2RCl *in 94% formic acid, in the presence of excess of calcium formate, at 15°.**

	t (min.)	5	10	15	20	25	30	40	50	60	∞ †
Me	*x*	3·77	6·1	8·4	9·25	—	12·05	14·0	—	18·0	32·3
a = 33·3	10^3k	2·4	2·0	1·9	1·6	—	1·5	1·4	—	1·3	1·8 ‡
Me	*x*	3·15	5·22	6·8	8·1	—	10·75	13·1	—	17·0	29·3
a = 30·2	10^3k	2·2	1·9	1·7	1·6	—	1·5	1·4	—	1·4	1·7 ‡
Et	*x*	8·15	10·85	13·55	16·0	17·75	19·7	24·8	—	—	32·5
a = 36·5	10^3k	5·0	3·5	3·2	2·9	2·8	2·7	3·0	—	—	3·3 ‡
Et	*x*	5·7	9·0	12·15	14·7	17·7	18·95	23·1	—	—	32·7
a = 35·0	10^3k	3·6	3·0	2·8	2·7	2·9	2·6	2·8	—	—	2·9 ‡
Pr^i	*x*	4·8	7·6	—	13·05	—	17·0	20·05	23·0	25·4	33·2
a = 36·6	10^3k	2·8	2·4	—	2·2	—	2·1	2·0	2·0	2·1	2·2 ‡
Pr^i	*x*	5·7	8·6	—	12·9	—	17·0	20·05	22·8	24·9	33·05
a = 36·35	10^3k	3·4	2·7	—	2·2	—	2·1	2·1	2·0	2·0	2·4 ‡
Bu^t	*x*	7·35	10·95	14·2	16·8	18·85	20·65	23·3	—	—	29·25
a = 31·25	10^3k	5·5	4·4	4·3	4·2	3·7	3·8	3·7	—	—	4·2 ‡
Bu^t	*x*	—	10·9	13·85	16·55	18·65	20·2	24·0	—	—	28·3
a = 30·7	10^3k	—	4·4	4·0	4·0	3·9	3·7	4·2	—	—	4·0 ‡

* *a* and *x* are the initial concentration of alkyl halide and the concentration of chloride ion after time *t* respectively. † 20—30 Hr. ‡ Average value of 10^3k.

in formic acid (m. p. 8·3°) (total volume 50 ml.) at 15° was added to a solution of alkyl halide (0·35—0·5 g.) in acetone (2·5 ml.) rapidly and with vigorous shaking; 5-ml. samples were pipetted into tubes which after specified periods were immersed in solid carbon dioxide; carbon tetrachloride (15 ml.) was added, the mixture was extracted with water (2 × 15 ml.), and the chloride was titrated (Volhard's method). The total halide content (ionised + labile organic) was estimated similarly, 5-ml. portions of formic acid solution being added directly to excess of silver nitrate solution (containing some ethanol).

The velocity coefficients are those for a first-order reaction opposed by one of the second order. (The occurrence of the reverse reaction between *tert.*-butyl alcohol and calcium chloride was observed in this medium.) The coefficients decrease as the reaction proceeds; for *tert.*-butyl chloride the *initial* coefficient agrees closely with the value obtained by Bateman and Hughes [17] for hydrolysis in slightly aqueous formic acid containing no calcium formate ($2·3 \times 10^{-2}$ min.$^{-1}$). Complete results appear in Table 5.

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317. *Adsorption of Complex Anions from Uranyl Sulphate Solution by Anion-exchange Resins.*

By T. V. ARDEN and G. A. WOOD.

At pH values below pH 2·5 uranium is adsorbed from sulphate solution by strong-base anion-exchange resins as a complex $UO_2(SO_4)_3^{4-}$. There is evidence that adsorption occurs by the formation of this ion on the resin by the addition of UO_2SO_4 to the resin sulphate, as well as by the normal exchange process. At pH values in excess of 2·5, the uranium loading of the resin increases, owing to the presence of increasing proportions of $U_2O_5(SO_4)_3^{4-}$ on the resin.

MOST of the work carried out on uranyl salt solutions has shown that uranium is present largely in cationic forms. McInnes and Longsworth [1] and Longsworth, Best, and Taub [2] showed that the UO_2^{2+} ion is present in acid solutions and is hydrolysed to form $U_2O_5^{2+}$ with increasing pH. Sutton [3] confirmed these results in non-complexing solutions, and showed that further hydrolysis gives $U_3O_8^{2+}$ and $U_3O_8{\cdot}OH^+$. He pointed out that in sulphate solutions his results would be modified by the effects of ion-pair formation. Betts

[1] McInnes and Longsworth, MDDC 911, Tech. Inf. Div., Oak Ridge, Tennessee.
[2] Longsworth, Best, and Taub, A380, M.R.C. of Canada, 1942.
[3] Sutton, *J.*, 1949, S 286.

and Michels [4] showed by spectrophotometric methods that in the concentration range 0·0—1·2M with respect to sulphate, the only complex present was the uncharged UO_2SO_4. This work has been criticised by Ahrland,[5] who has calculated formation constants for UO_2SO_4, $UO_2(SO_4)_2^{2-}$, and $UO_2(SO_4)_3^{4-}$ from the results of potentiometric and spectrophotometric studies. Nevertheless, his work suggests that, in dilute solutions at least, the predominant complex is UO_2SO_4 and that anionic complexes exist only in low concentrations. The absence of significant concentrations of anions in solution is confirmed by Arden,[6] who showed by conductometric and potentiometric methods that the properties of uranyl sulphate solutions from pH 1·5 to pH 5·0 can be explained almost completely by the postulation of Sutton's condensed cations [3] and the corresponding uncharged sulphates.

All evidence thus points to the virtual absence of anionic complexes from uranyl sulphate solutions. Nevertheless, it has been found that uranium is strongly adsorbed from these solutions by strong-base anion-exchange resins. The purpose of this work, which was commenced at the Chemical Research Laboratory in 1950, has been to study the nature of the anions adsorbed and the adsorption mechanism.

Experimental

The resins used were Amberlite IRA-400, De-Acidite FF, and some samples made at the Chemical Research Laboratory. All these materials are stated to be cross-linked polystyrene, containing quaternary groups of the benzyltrimethylammonium type; and no significant difference between them could be found for this purpose.

The chloride capacities and dry weights recorded were in each case measured on the actual column of resin used for uranium adsorption, by reconverting it into the chloride form at the end of each test, and finally drying and weighing it in this form. By this means, errors due to varying moisture content were prevented, without introducing others by drying the resin samples before use.

All tests were carried out in downward flowing columns, which were run to final equilibrium. In the experiments used for capacity and charge-balance comparisons, the columns were contained in centrifuge tubes closed with filter discs. To avoid errors due to changes in conditions, the resin was not washed at the end of each test, but was freed from excess of solution by centrifuging, the measured ionic content of the resin being corrected for the effect of remaining interstitial liquor by the method of Kraus and Moore.[7] This correction was negligible in cases where the sulphate content of the solution used was less than 0·5M, and in no case exceeded 2%.

Determinations were made first of uranium and sulphate taken up by Amberlite IRA-400 resin in the sulphate form, on passage of a pure uranyl sulphate solution (0·098M) containing a small excess of sulphate through a column of the resin (2·40 g. dry weight). The results are shown in Table 1.

Table 1.

Effluent (ml.)	50	100	150	200	250	300	350	400	450	500
SO_4 adsorbed (mmoles)	0·497	0·495	0·442	0·268	0·188	0·136	0·108	0·091	0·075	0·062
UO_2 adsorbed (mmoles)	0·491	0·488	0·442	0·270	0·169	0·136	0·107	0·082	0·077	0·060
$SO_4 : UO_2$ ratio	1·01	1·02	1·00	0·99	1·11	1·00	1·01	1·11	0·97	1·03

Determinations of the total uranium uptake of several different types of quaternary ammonium resins were carried out by using 0·005—0·01M-uranyl sulphate solutions, at pH 1·7—2·0. This pH range was chosen since it has been shown by Longsworth *et al.*[1] that, above pH 2·0, there is a measurable degree of hydrolysis of the UO_2^{2+} ion to give the condensed $U_2O_5^{2+}$ ion. Typical results are given in Table 2. The significance of the term n is considered on p. 1599.

The effect of sulphate concentration on uranium adsorption was measured by the centrifuge technique, with a sample of De-Acidite FF having a capacity of 3·70 mequiv./g. The solutions used were in each case 0·005M with respect to UO_2SO_4, with varying concentrations of sulphate added as the magnesium salt. Two series of tests were carried out, at pH 1·8 and 2·5. The ratio of chloride desorbed to uranium adsorbed, and the ratio of sulphate to uranium adsorbed,

[4] Betts and Michels, *J.*, 1949, S 276.
[5] Ahrland, *Acta Chem. Scand.*, 1951, **5**, 1151.
[6] Arden, *J.*, 1949, S 60; Thesis, London, 1953.
[7] Kraus and Moore, *J. Amer. Chem. Soc.*, 1953, **75**, 1497.

TABLE 2.

	Capacity Cl^- (mequiv./g.)	UO_2 (mmoles/g.)	Mol. ratio Cl : UO_2	n
De-Acidite FF	3·58	0·878	4·08	3·06
Amberlite IRA-400 ...	3·60	0·915	3·94	2·97
De-Acidite FF	3·60	0·913	3·95	2·95
Amberlite IRA-400 ...	3·71	0·918	4·04	3·03
De-Acidite FF	3·87	0·968	4·00	3·00
AMX 35 (CRL)	4·1	0·963	4·26	3·21
AMX 36 (CRL)	4·8	1·073	4·44	3·33

FIG. 1.

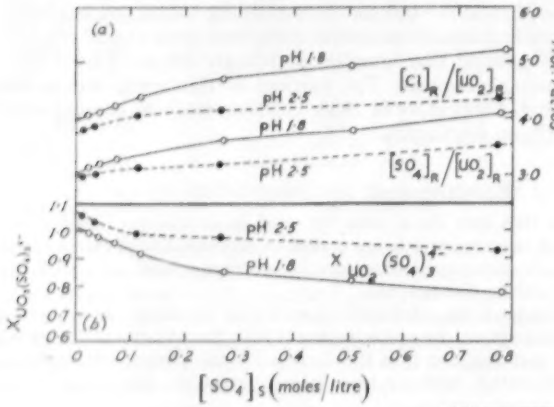
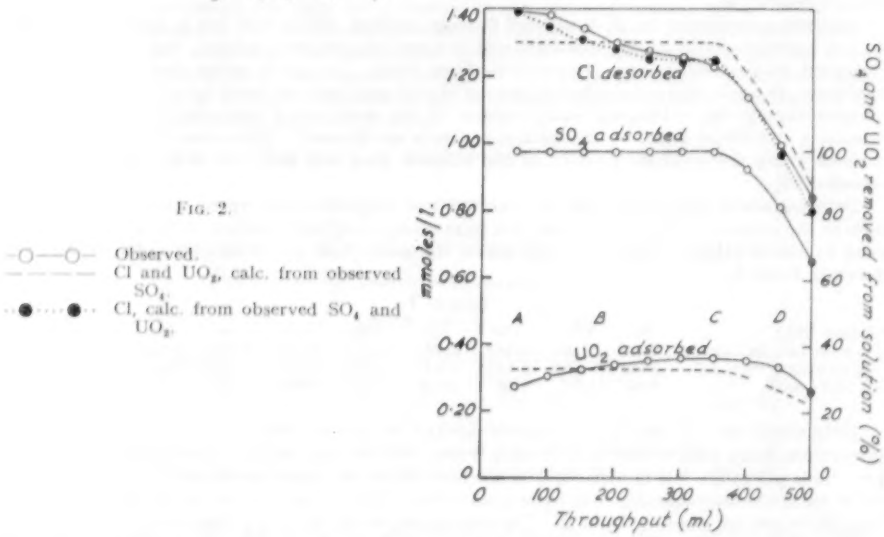


FIG. 2.



—○—○— Observed.
– – – – Cl and UO_2, calc. from observed SO_4.
·●·····●·· Cl, calc. from observed SO_4 and UO_2.

are given in Fig. 1*a*, and the calculated proportion of resin capacity occupied by a postulated ion $UO_2(SO_4)_3^{4-}$ is plotted in Fig. 1*b*.

This test gave the final equilibrium results. The adsorption process was studied by passing through a column of IRA-400 (chloride form, 2·4 g.) a solution 0·00946M with respect to UO_2 and 0·00972M with respect to SO_4. The reduction in concentration of uranium and sulphate in the emerging fractions, together with the concentration of chloride produced, are plotted in Fig. 2 as continuous curves.

The variations of uranium and sulphate loadings with pH were also measured by the

centrifuge technique, using a column containing De-Acidite FF having a chloride capacity of 3·62 mequiv./g., and solutions 0·005M with respect to UO_2SO_4, together with sufficient sulphuric acid or sodium hydroxide to adjust the pH to a series of values from 0·5 to 5·0, above which precipitation of uranyl hydroxide occurred. The uranium loadings are plotted in Fig. 3, and the significance of sulphate adsorption is considered in the discussion of Tables 4 and 5.

A similar series of tests was carried out on the adsorption of sulphate and bisulphate from unbuffered solutions of sulphuric acid, containing no uranium, adjusted to have the same free sulphate content as the corresponding uranium solutions. The sulphate content varied from 0·0044M at pH 2·5 to 0·248M at pH 0·58. These results are plotted in Fig. 4.

FIG. 3.

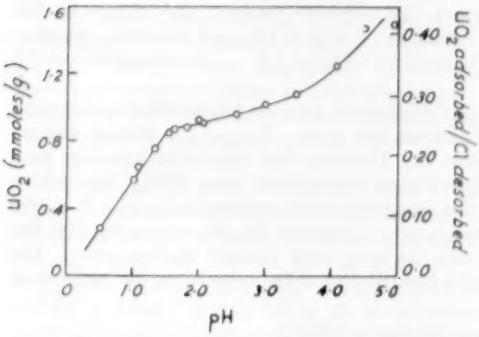
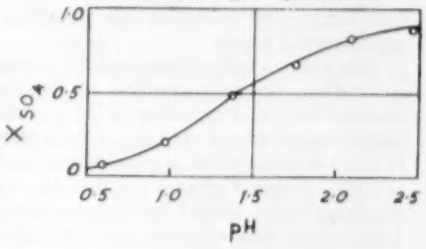


FIG. 4. Ratio, SO_4/HSO_4 on resin.



DISCUSSION

The results given in Table 1 show that, during the adsorption of uranium on a sulphate-form resin, equimolecular amounts of uranium and sulphate are taken up at all stages, suggesting that the complex on the resin is of the type $UO_2(SO_4)_n^{2-2n}$, where $n > 2$. If it is assumed that the resin is saturated with one ionic type, then the penultimate column of Table 2 gives the charge on this ion, *viz.*, $(2 - 2n)$, from which is calculated the $SO_4 : UO_2$ ratio, n. In tests with 65 different resin samples, this value showed a maximum variation of 2·95—3·06, except with resin samples of exceptionally high chloride capacity, in which the complete adsorption of uranium was apparently prevented by steric hindrance between the large complex anions, giving high values of n. The two lowest members of the series are $UO_2(SO_4)_2^{2-}$ and $UO_2(SO_4)_3^{4-}$, the measured value of n suggesting that the latter is adsorbed, although the same value would be given if the resin contained at equilibrium an equal mixture of $UO_2(SO_4)_2^{2-}$ and SO_4^{2-}.

Two possible mechanisms exist for the adsorption of the uranyl trisulphate ion. The first is the formation of the complex in solution, followed by its exchange with sulphate on the resin :

$$UO_2^{2+} + 3SO_4^{2-} \rightleftharpoons UO_2(SO_4)_3^{4-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$2R_2SO_4 + UO_2(SO_4)_3^{4-} \rightleftharpoons R_4UO_2(SO_4)_3 + 2SO_4^{2-} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$K_1 = [UO_2(SO_4)_3^{4-}]_S/[UO_2^{2+}]_S[SO_4^{2-}]_S^3$$

$$K_2 = [UO_2(SO_4)_3^{4-}]_R[SO_4^{2-}]_S^2/[SO_4^{2-}]_R^2[UO_2(SO_4)_3^{4-}]_S$$

Whence $[UO_2(SO_4)_3^{4-}]_R/[SO_4^{2-}]_R^2 = K_1K_2[UO_2^{2+}]_S[SO_4^{2-}]_S$

By this process, therefore, at constant uranium concentration in solution, the uranium uptake on the resin would decrease with decreasing sulphate concentration in solution. No such decrease can be observed experimentally; and it must be deduced that if the mechanism of equations (1) and (2) operates, the product K_1K_2 is so large that $[SO_4^{2-}]_R^2$ is reduced to an undetectable level, irrespective of the value of $[SO_4^{2-}]_S$. A similar reasoning can be applied to the possible lower complex $UO_2(SO_4)_2^{2-}$; and it follows that

there is effectively a complete absence of competition for active groups on the resin, which must, under the conditions of these tests, always become saturated with the uranium complex.

The second possible mechanism is by the addition reaction (3):

$$2R_2SO_4 + UO_2SO_4 \rightleftharpoons R_4UO_2(SO_4)_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Undissociated UO_2SO_4, being uncharged, would be able to enter the resin freely, without hindrance by the Donnan membrane effect. Equation (3) implies lack of competition for the resin sites, and complete saturation of the resin by the uranium complex irrespective of sulphate concentration. By either of these mechanisms, therefore, the limiting values for $[SO_4]_R/[UO_2]_R$ and $[Cl]_R/[UO_2]_R$ represent the sulphate content and charge of the complex ion. At pH 1·8, these limiting values are 3·0 and 4·0, and the only uranium complex present in measurable quantities is therefore $UO_2(SO_4)_3^{4-}$. The results at pH 2·5 are discussed below.

Since it has been shown that the presence of sulphate in solution has no effect on uranium adsorption, the mole-fraction of the complex on the resin, $X_{UO_2(SO_4)_3^{4-}}$, should remain constant at 1·0, irrespective of $[SO_4]_S$, whereas Fig. 1*b* shows that this value decreases with increasing measured $[SO_4]_S$. This decrease is due to competition from HSO_4^- ions which at pH 1·8 account for approximately half the free sulphate in solution ($K_{HSO_4} = 2 \times 10^{-2}$ at 18°). Table 3 gives a calculation of the charges accounted for, by assuming that the bisulphate and uranyl trisulphate anions are the only ones present on the resin. The total agrees well with the measured chloride capacity of 3·78 mequiv./g. for this resin sample.

TABLE 3. *Charge balance at* pH 1·8.

Solution		Resin (mmole/g.)				Charge (mequiv./g.)		
			Combined	Total	Free		$UO_2(SO_4)_3^{4-}$	
UO_2 (mole/l.)	SO_4 (mole/l.)	UO_2 (measured)	SO_4 ($3 \times UO_2$)	SO_4 (measured)	SO_4 (diff.)	HSO_4	($4 \times UO_2$)	Total
0·0048	0·780	0·723	2·17	2·92	0·75	0·75	2·99	3·67
,,	0·509	0·766	2·30	2·88	0·58	0·58	3·07	3·65
,,	0·270	0·801	2·41	2·88	0·47	0·47	3·21	3·68
,,	0·119	0·861	2·58	2·92	0·34	0·34	3·44	3·78
,,	0·071	0·899	2·70	2·92	0·22	0·22	3·60	3·82
,,	0·044	0·924	2·77	2·92	0·15	0·15	3·69	3·84
,,	0·023	0·942	2·83	2·93	0·10	0·10	3·77	3·87

Similar calculations were carried out, by assuming that (*a*) $UO_2(SO_4)_3^{4-}$ and SO_4^{2-}, or (*b*) $UO_2(SO_4)_2^{2-}$ and SO_4^{2-} were the only ions present. In each case the total charge increased with increasing values of $[SO_4]_S$, from 3·93 to 4·49. These differences are much greater than the experimental error, and it is concluded that no combinations of these ions can account for the observed results. The only other possibility, that of $UO_2(SO_4)_2^{2-}$ and HSO_4^-, gives very low values.

The adsorption of uranium as a complex sulphate requires that removal of uranium from a stoicheiometric uranyl sulphate solution by a chloride-form resin cannot be complete. This is shown to be true in Fig. 2, which also gives evidence of the mechanism of adsorption. The values calculated for uranium and chloride exchange, based on the observed sulphate figures, with the assumption that the trisulphate anion is adsorbed throughout, are shown as broken lines.

The observed values are sufficiently close to the calculated figures to confirm that the overall process is that of the adsorption of the trisulphate anion; but in the early part of the run, in the region *AB*, the uranium adsorption is slightly lower than the theoretical value, the chloride desorption being higher. It follows that, in this region, sulphate is being partly adsorbed in place of the uranium complex, and is thereby displacing two chloride ions for each sulphate adsorbed, instead of 1·33. This phenomenon would occur if the adsorption of uranium on a given site required the prior conversion of this site into the sulphate form, followed by the addition of UO_2SO_4 (equation 3). The same effect would be given by a normal ion-exchange process if the rate of the sulphate–chloride

exchange were higher than the rate of the uranium anion-chloride exchange. The two processes can be distinguished by the next part of the curve. In the region *BC* uranium adsorption exceeds the calculated value, while chloride emission is reduced. This effect, which means that a greater degree of exchange is apparently taking place without any corresponding emission of ions from the resin, can only be explained by the addition of uranyl sulphate molecules on to resin sites already in the sulphate form, this process being superimposed on the adsorption of the trisulphate molecule by either of the mechanisms discussed above. The fact that in the region *CD* uranium adsorption continues unchanged, although sulphate has broken through and chloride exchange is decreasing rapidly, gives further confirmation of this process.

The dotted curve in Fig. 2 gives the calculated chloride emission value based on the assumption that uranium is adsorbed as $UO_2(SO_4)_3^{4-}$ in the region *AB*, the excess of sulphate being present as SO_4^{2-}. In the remainder of the curve it is assumed that uncharged uranyl sulphate and the trisulphate are adsorbed together, the ratios of the two being simply calculated from the measured uranium and sulphate values. Summation of the charges on the anions present gives the calculated curve, which is in good agreement with the observed value.

All the results so far considered have been of measurements at pH 1·7—2·0. Fig. 3 shows the effect of varying pH; and it is clear that the complete adsorption of $UO_2(SO_4)_3^{4-}$ which has been postulated occurs only in the region previously chosen. The decrease in loading below pH 2·0 can be explained by the increasing effect of competition from bisulphate ions. It is shown in Fig. 4 that the reduction in sulphate adsorption below pH 2·5 is similar to the fall in uranium loading, supporting the theory that uranium is adsorbed on sites in the sulphate, but not the bisulphate form.

TABLE 4.

	Resin (mmole/g.)				Charge (mequiv./g.)		
						$UO_2(SO_4)_3^{4-}$	
Solution pH	UO_2 (measured)	Combined SO_4 ($3 \times UO_2$)	Total SO_4 (measured)	Free HSO_4 (diff.)	HSO_4	($4 \times UO_2$)	Total
0·52	0·276	0·83	3·21	2·38	2·38	1·10	3·49
1·01	0·573	1·72	3·10	1·28	1·28	2·29	3·57
1·32	0·738	2·21	2·90	0·68	0·68	2·95	3·63
1·61	0·840	2·52	2·87	0·35	0·35	3·36	3·71
1·82	0·866	2·59	2·80	0·21	0·21	3·47	3·68
2·01	0·903	2·71	2·67	−ve	—	3·61	3·61

Table 4 gives the total of ion-active groups accounted for, on the assumption that $UO_2(SO_4)_3^{4-}$ and HSO_4^- are the only ions adsorbed on the resin. Over the pH range 0·5—2·0, the results agree well with the total measured chloride capacity of 3·62 mequiv./g., the maximum difference being 0·13, or 3·6%.

The pH curve for values higher than pH 2·5 cannot be explained on the basis of the quadrivalent complex, since the total resin loadings are higher than the saturation value for this ion. These values could be given by the bivalent $UO_2(SO_4)_2^{2-}$ ion, but there is no theoretical reason why increasing pH should favour the adsorption of this ion at constant uranium and sulphate concentration.

A more probable explanation is given if it is assumed that the condensed uranyl ions which occur with increasing pH can form complexes of the type $U_2O_5(SO_4)_3^{4-}$, similar to that formed by the simple UO_2^{2+} ion. As the effective charge per uranyl group is reduced, the increase in resin loading with pH is explained.

Table 5 gives the ratios of uranium and sulphate uptake to chloride capacity, which would be given by saturation of a resin (capacity 3·62 mequiv./g.) with each of the possible ions which can be formed by combination of sulphate with the various uranyl cations. The observed values at pH 2·0 and 5·0 are included. A number of different mixtures of complex anions can be posulated to account for the observed uranium uptake at high pH, and two typical examples are given.

All bivalent complexes give SO_4 : Cl ratios of 1 : 1, the ratios for quadrivalent complexes being 0·75 : 1. The observed results at pH 5·0 have varied by ±5%, but in no case have

they exceeded the 0·75 : 1 ratio. It is therefore improbable that $UO_2(SO_4)_2^{2-}$ is present on the resin under these conditions, and the enhancement of uranium adsorption must be due to an increasing proportion of $U_2O_5(SO_4)_3^{4-}$ with increasing pH.

TABLE 5.

	Ratios			Total mmole/g		
	UO_2	SO_4	Cl	UO_2	SO_4	Cl
$UO_2(SO_4)_2^{2-}$	0·5	1·0	1·0	1·81	3·62	3·62
$UO_2(SO_4)_3^{4-}$	0·25	0·75	1·0	0·91	2·72	3·62
$U_2O_5(SO_4)_2^{2-}$	1·0	1·0	1·0	3·62	3·62	3·62
$U_2O_5(SO_4)_3^{4-}$	0·5	0·75	1·0	1·81	2·72	3·62
$U_3O_8(SO_4)_2^{2-}$	1·33	1·0	1·0	4·80	3·62	3·62
$U_3O_8(SO_4)_3^{4-}$	0·75	0·75	1·0	2·72	2·72	3·62
Observed at pH 2·0	0·25	0·75	1·0	0·91	2·72	3·62
Observed at pH 5·0	0·41	0·69	1·0	1·50	2·48	3·62
$1UO_2(SO_4)_3^{4-} : 3{\cdot}8UO_2(SO_4)_2^{2-}$	0·41	0·90	1·0	1·50	3·25	3·62
$1UO_2(SO_4)_3^{4-} : 1{\cdot}9U_2O_5(SO_4)_2^{4-}$	0·41	0·75	1·0	1·50	2·72	3·62

The observed values could also be explained by the presence of increasing amounts of precipitated uranyl hydroxide on a resin remaining in the $UO_2(SO_4)_3^{4-}$ form throughout. This explanation is considered improbable, since no precipitate could be detected visually in the experiments recorded, whereas it was shown, in tests carried out at a slightly higher pH, that a quantity of precipitate which made no significant difference to the measured uranium loading was clearly visible. The polyuranate anions of the type $U_3O_8(OH)_3^-$ and $U_3O_8(OH)_4^{2-}$, suggested both by Sutton [3] and by Arden,[6] which would also have this effect, were shown by Arden to be significant only above pH 7·0.

These considerations of the effect of pH give the reasons for the difference in results at pH 2·5 as shown by the broken curves of Fig. 1. This pH was chosen as being the point at which both HSO_4^- adsorption (Fig. 4) and $U_2O_5(SO_4)_3^{4-}$ adsorption (Fig. 3) were low. The reduced effect of bisulphate results in a reduction in the slope of the broken curves, as compared with the continuous curves measured at pH 1·8. The apparent anomaly in the value for $X_{UO_2(SO_4)_3^{4-}}$ at low sulphate concentrations is also explained. Table 6 gives the charge balance, calculated on the assumption that at pH 2·5 the uranyl anions are present in all tests in the ratio $18UO_2(SO_4)_3^{4-} : 1U_2O_5(SO_4)_3^{4-}$, the value which corresponds with the observed uranium uptake in the lowest line of the table. Then the mean charge per uranyl group is −3·8 and the mean $SO_4 : UO_2$ ratio 2·85. The free sulphate is assumed to be present as HSO_4^-. The total charge accounted for is in good agreement in every case with the total chloride capacity of the resin sample used, *viz.*, 3·62 mequiv./g.

TABLE 6. *Charge balance at* pH 2·5.

Solution		Resin (mmoles/g.)				Charge		
			Combined	Total			U complex	
UO_2 (mole/l.)	SO_4 (mole/l.)	UO_2 measured	SO_4 (2·85 × UO_2)	SO_4 (measured)	Free SO_4	HSO_4	(3·80 × UO_2)	Total
0·048	0·771	0·835	2·38	2·97	0·55	0·55	3·09	3·64
,,	0·266	0·879	2·50	2·80	0·30	0·30	3·25	3·55
,,	0·117	0·895	2·55	2·70	0·24	0·24	3·31	3·55
,,	0·035	0·930	2·65	2·80	0·15	0·15	3·44	3·59
,,	0·011	0·953	2·72	2·82	0·10	0·10	3·53	3·63

It is concluded that the whole of the observed phenomena can be explained by the assumptions that, at pH values below 2·0, only $UO_2(SO_4)_3^{4-}$ and HSO_4^- are present on the resin, neither $UO_2(SO_4)_2^{2-}$ nor SO_4^{2-} being adsorbed in measurable quantities. The increase in loading at higher pH values is explained by the presence of $U_2O_5(SO_4)_3^{4-}$. There is nevertheless no conflict with the work of Ahrland,[5] who postulated an equilibrium in solution between $UO_2(SO_4)_2^{2-}$ and $UO_2(SO_4)_3^{4-}$. It is generally agreed that uranium exists in sulphate solution almost entirely as the uranyl cation, or as undissoicated uranyl sulphate, and that the complex anions exist in very low concentrations. Under these conditions, it is to be expected that the affinity of the quadrivalent complex will be so

much higher than that of the bivalent complex, that the equilibrium in solution will be almost completely displaced in the presence of the resin.

Since the completion of this work O'Connor's [8] studies on the same subject have been declassified. Ahrland's equilibrium constants were used as a basis for the calculations of the equilibrium concentrations of the various anions on the resin. Although in general agreement with us that the predominant species present is $UO_2(SO_4)_3^{4-}$, O'Connor has calculated that under conditions similar to ours, up to 10% of the resin sites may be occupied by $UO_2(SO_4)_2^{-2}$. The calculations are based upon the fundamental assumption that the HSO_4^-–SO_4^{2-} equilibrium on the resin, which was studied separately, is unchanged by the presence of the complex anions. It is considered unlikely that this can be true in view of the agreement between O'Connor and ourselves that almost, if not all, the sulphate on the resin is present as complex. O'Connor's further deduction that solutions containing high uranium concentrations with low free sulphate yield high proportions of $UO_2(SO_4)_2^{2-}$ on the resin, is not in conflict with our results. From general considerations of mass action effects in a 2 : 4-valent system it is to be expected that increasing ionic strength would favour the lower complex.

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[8] O'Connor, T.O. ACCO-61 (U.S.A.E.C.), 1954.

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318. *Organometallic Compounds of the Alkali Metals. Part VI.* Evidence for the Formation of Free Alkyl Radicals during Certain Wurtz Reactions. Homolytic Reactions between Alkyl-lithium Compounds and Alkyl Halides.†*

By D. Bryce-Smith.

*iso*Propylbenzene has been used to detect the formation of free alkyl radicals during certain reactions of the Wurtz type. With *n*-butyl iodide at 130°, the tendency to form free *n*-butyl radicals decreases in the order lithium > sodium > potassium. The free radicals are largely, if not entirely, produced by a reaction of the type, RM + RHal ⟶ 2R· + MHal, rather than RHal + M ⟶ R· + MHal. The evidence indicates that free radicals play only a minor part in the formation of the usual Wurtz coupling and disproportionation products.

n-Butyl-lithium with iodine gives *n*-butyl iodide, which may then react with excess of *n*-butyl-lithium to give *n*-butyl radicals.

n-Butyl radicals, from *n*-butyl bromide and *n*-butyl-lithium, are relatively unreactive towards benzene, giving a trace of *n*-butylbenzene but no diphenyl.

Although it is well known from the work of Polanyi and his co-workers (reviewed by Warhurst [1]) that alkyl halides with sodium vapour at elevated temperatures and low pressures produce free alkyl radicals, it has for long been uncertain whether a comparable reaction occurs in solution at lower temperatures under the usual conditions of the Wurtz

* Part V, *J.*, 1955, 1712.

† An account of some of the present results was presented at the Symposium on Organometallic Compounds, Manchester, in April, 1955: see *Nature*, 1955, **176**, 60.

[1] Warhurst, *Quart. Rev.*, 1951, **5**, 44.

reaction. Two basically different mechanisms have been proposed and supported by various workers :

$$\begin{array}{lll} \text{(A)} & \text{(i)} & \text{RBr} + \text{Na} \longrightarrow \text{R}\cdot + \text{NaBr} \\ & \text{(ii)} & 2\text{R}\cdot \longrightarrow \text{R–R} \\ \text{(B)} & \text{(i)} & \text{RBr} + 2\text{Na} \longrightarrow \text{RNa} + \text{NaBr} \\ & \text{(ii)} & \text{RNa} + \text{RBr} \longrightarrow \text{R–R} + \text{NaBr} \end{array}$$

The free-radical mechanism (A) was first suggested by Schlubach and Goes [2] but, although its possibility has received much subsequent discussion, there seems to be little definite experimental support. The " sodium flame " reactions [1] and the Ullmann reaction [3] both involve free radicals, and rather unsafe analogies have sometimes been noted between these and the Wurtz reaction. Bachmann and Clarke [4] isolated *o*-terphenyl and triphenylene from the reaction between chlorobenzene and sodium at 130° and regarded the production of these compounds as evidence for the intermediate formation of free phenyl radicals; but Dewar [5] and Morton, Davidson, and Hakan [6] have suggested alternative non-radical explanations. In the light of recent work,[7] it seems that the reaction of chlorobenzene with phenylsodium might well lead to the formation of " benzyne," C_6H_4, the trimerisation of which to triphenylene has been reported by Luttringhaus and Schubert.[7] Kharasch, Holton, and Nudenberg [8] treated *sec.*- and *tert.*-butyl bromide with sodium in the presence of isoprene. They obtained products which suggested an interaction between the free alkyl radicals and isoprene, but appeared not to regard their results as wholly conclusive.

Mechanism (B) seems to be more widely supported. The formation of alkali-metal alkyls during Wurtz-type reactions has been demonstrated on many occasions, and by suitable choice of conditions, alkyls of lithium,[9] sodium,[10] and potassium [11] have been prepared. Morton and his co-workers [6] concluded from an extensive investigation that all the coupling and disproportionation products of Wurtz reactions could be accounted for without an assumption of free-radical intermediates, although they did not wholly exclude the possibility that free radicals play a small part (cf. Morton and Brachman; [12] Morton and Cluff [13]). Many workers [14] have studied the coupling and disproportionation reactions which occur between alkali-metal alkyls and alkyl halides. The results, which are complex, appear not to have suggested the possibility of free-radical intermediates.

In the present work, *iso*propylbenzene has been used as a detector for possible free-radical intermediates in the Wurtz reaction and in some related reactions. In earlier Parts of this series [15, 16] it was shown that *iso*propylbenzene does not produce free alkyl radicals during its reactions with alkali-metal alkyls, and the difficulties inherent in the use of isoprene as a radical detector are therefore avoided.

Experimental

*iso*Propylbenzene was purified by shaking B.D.H. material with portions of concentrated sulphuric acid until the acid remained almost colourless, washing, drying, and then distilling it over calcium hydride and sodium through a 180-cm. column of Fenske helices. A middle fraction boiling over 0·3° was used. The hydrocarbon was stored over a little powdered calcium hydride to keep it dry and to prevent the formation of peroxide. (We have found sodium

[2] Schlubach and Goes, *Ber.*, 1922, **55**, 2889.
[3] (*a*) Rapson and Shuttleworth, *Nature*, 1941, **147**, 675; (*b*) Nursten, *J.*, 1955, 3081.
[4] Bachmann and Clarke, *J. Amer. Chem. Soc.*, 1927, **49**, 2089.
[5] Dewar, " Electronic Theory of Organic Chemistry," Oxford, 1949, pp. 258—259.
[6] Morton, Davidson, and Hakan, *J. Amer. Chem. Soc.*, 1942, **64**, 2242.
[7] Lüttringhaus and Schubert, *Naturwiss.*, 1955, **42**, 17; Roberts *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 3290.
[8] Kharasch, Holton, and Nudenberg, *J. Org. Chem.*, 1955, **20**, 920.
[9] Ziegler and Colonius, *Annalen*, 1930, **479**, 135.
[10] Morton and Hechenbleikner, *J. Amer. Chem. Soc.*, 1936, **58**, 1697.
[11] Morton, Brown, Holden, Letsinger, and Magat, *ibid.*, 1945, **67**, 2224.
[12] Morton and Brachman, *ibid.*, 1954, **76**, 2973, 2980.
[13] Morton and Cluff, *ibid.*, 1952, **74**, 4056; 1953, **75**, 134.
[14] (*a*) Morton and Richardson, *ibid.*, 1940, **62**, 123; (*b*) Whitmore and Zook, *ibid.*, 1942, **64**, 1783; (*c*) Ulrich *et al.*, *ibid.*, 1950, **72**, 5127, 5130, 5132; (*d*) Letsinger and Traynham, *ibid.*, p. 849; (*d*) Cristol *et al.*, *ibid.*, 1951, **73**, 810, 813. [Further references are there cited.]
[15] Bryce-Smith, *J.*, 1955, 1712.
[16] Bryce-Smith, *J.*, 1954, 1079.

hydride and calcium hydride to be very useful in this respect for a number of hydrocarbons and ethers.) Alkyl halides were purified as in Part I.[17] Alkyl iodides contained no free iodine. Solutions of alkyl-lithium compounds in aromatic solvents were prepared as in Part II :[18] free metal and lithium halides were excluded.

Alkali metals were used in the form of wire (0·5 mm. diam.), except where otherwise stated. All reactions were carried out under nitrogen, with stirring.

It was not found practicable to separate *n*-octane (b. p. 126°) from *iso*propylbenzene (b. p. 151°) by fractional distillation. A composition–refractive index curve was constructed from which the proportions of *n*-octane in the experimental mixtures with *iso*propylbenzene were found.

The yields of 2 : 3-dimethyl-2 : 3-diphenylbutane refer to material of m. p. >114°. The pure compound, m. p. 118—118·5°, was obtained by recrystallisation from ethyl alcohol or, in difficult cases, by passing a solution in light petroleum through a column of alumina. Mixed m. p.s were always taken.

Reactions between Alkali Metals and Alkyl Iodides.—(a) *Sodium and ethyl iodide.* A dispersion of sodium (2·0 g., 0·087 g.-atom) in *iso*propylbenzene (35 g.) was stirred with ethyl iodide (15·6 g., 0·1 mole) at 90—95° for 20 hr. The product was filtered through sintered glass under nitrogen. The material (*ca.* 0·3 g.), b. p. >160°, partly crystallised after 10 days. Addition of a little 1 : 1 methanol–ethanol gave 2 : 3-dimethyl-2 : 3-diphenylbutane (0·03 g., 0·3%).

(b) *Lithium and* n-*butyl iodide.* (i) At 95°. *n*-Butyl iodide (9·2 g., 0·05 mole) was heated with lithium (1·05 g., 0·15 g.-atom) in *iso*propylbenzene (24 g.) for 18 hr. The product was filtered as in method (a). The yields of 2 : 3-dimethyl-2 : 3-diphenylbutane and *n*-octane were 1·1 g. (19%) and 1·0 g. (35%) respectively.

(ii) At 130°. The previous experiment was repeated at 130° with *n*-butyl iodide (11·0 g., 0·06 mole) and lithium (1·25 g., 0·18 g.-atom) in *iso*propylbenzene (29 g.). Butane (20%) and butene (10%) were collected in a trap at −25°. Traces of lower-boiling hydrocarbons appeared to be also formed, suggesting slight fragmentation of butyl radicals. Titration of an aliquot[18] showed that 0·003 mole (5%) of a soluble organometallic species was formed, possibly *n*-butyl-lithium. After hydrolysis, the yields of 2 : 3-dimethyl-2 : 3-diphenylbutane and *n*-octane were 1·2 g. (18%) and 0·8 g. (24%) respectively.

(c) *Sodium and* n-*butyl iodide.* (i) at 25°. *n*-Butyl iodide (9·2 g., 0·05 mole) was added during 1 hr. to sodium (3·5 g., 0·152 g.-atom) in *iso*propylbenzene (24 g.). The blue product was kept at *ca.* 20° for 2 days. A small portion gave a negative test for butylsodium.[19] Butane (1·6%) and butene (1·4%) were pumped off. After hydrolysis, *n*-octane (2·35 g., 83%) was obtained, but no trace of 2 : 3-dimethyl-2 : 3-diphenylbutane could be detected.

(ii) The previous experiment was repeated on a larger scale, and with an excess of *n*-butyl iodide. *n*-Butyl iodide (22·0 g., 0·12 mole), sodium (2·3 g., 0·1 g.-atom), and *iso*propylbenzene (48 g.) gave butane (5·7%), butene (5·3%), and *n*-octane (4·7 g., 69%); but again, no 2 : 3-dimethyl-2 : 3-diphenylbutane was found. The estimation of *n*-octane was complicated by the necessity to remove the excess of *n*-butyl iodide (b. p. 130°) by heating the *iso*propylbenzene–octane mixture with alcoholic potassium hydroxide. The figure quoted may be rather low.

(iii) At 130°. *n*-Butyl iodide (13·8 g., 0·075 mole) was added during 30 min. to sodium (5·2 g., 0·225 g.-atom) in *iso*propylbenzene (36 g.). After a further 15 min., the grey product was briefly heated at 150° in order to expel all butane and butene. Butane (0·46 g., 10·5%), butene (0·15 g., 3·5%), *n*-octane (2·6 g., 61%), and 2 : 3-dimethyl-2 : 3-diphenylbutane (0·11 g., 1·2%) were obtained.

(iv) Experiment (*c*) (ii) was repeated, but, before addition of water, the blue reaction product was heated for 1 hr. at 130°, at which temperature all colour was rapidly discharged. No 2 : 3-dimethyl-2 : 3-diphenylbutane was obtained.

(d) *Potassium and* n-*butyl iodide at* 130°. *n*-Butyl iodide (22·0 g., 0·12 mole) was added during 30 min. to potassium (3·9 g., 0·1 g.-atom) in *iso*propylbenzene (48 g.). *n*-Octane (2·0 g., 29%) was formed. Distillation at 20 mm. gave fractions, b. p. (i) 120—130° (1·0 g.) and (ii) 130—160° (0·5 g.), together with an oily residue (0·5 g.). Fraction (i) was probably largely *n*-butyl-*iso*propylbenzenes (Found : C, 88·1; H, 11·35. Calc. for $C_{13}H_{20}$: C, 88·6; H, 11·4%). Treatment with ethanol gave, after prolonged storage, 2 : 3-dimethyl-2 : 3-diphenylbutane (2 mg., 0·02%). This was not quite pure, having m. p. 111—113° and mixed m. p. 112—114°.

[17] Bryce-Smith and Turner, *J.*, 1950, 1975.
[18] Bryce-Smith and Turner, *J.*, 1953, 861.
[19] Gilman and Schulz, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

Reactions between Alkyl Halides and Alkali-metal Alkyls.—(e) n-*Butyl chloride and* n-*butyl-lithium.* A solution of *n*-butyl-lithium (0·043 mole) in *iso*propylbenzene (41 g.) was heated with *n*-butyl chloride (4·15 g., 0·045 mole) at 95° (inner temp.) for 6 days. There was an induction period of 1 hr. before the solution became turbid owing to precipitation of lithium chloride. Titration of an aliquot portion of the supernatant liquid showed that only a trace of *n*-butyl-lithium remained. After treatment with water, the separated and dried organic layer was fractionated. The fraction of b. p. 125—151° contained *n*-octane (1·4 g., 29%). The colourless material, b. p. >160° (1·66 g.), solidified on cooling. Recrystallisation from methanol gave pure 2 : 3-dimethyl-2 : 3-diphenylbutane (1·21 g., 12%).

(f) n-*Butyl bromide and* n-*butyl-lithium.* (i) At 20—25°. *n*-Butyl bromide (12 g., 0·088 mole), *n*-butyl-lithium (0·043 mole), and *iso*propylbenzene (16 g.) gave, after five days, *n*-octane (2·5 g., 51%) and 2 : 3-dimethyl 2 : 3-diphenylbutane (1 g., 9%). The induction period was 2 hr.

(ii) At 60°. *n*-Butyl bromide (5·8 g., 0·0425 mole), *n*-butyl-lithium (0·0405 mole), and *iso*propylbenzene (39 g.) gave, after 3 days, *n*-octane (1·8 g., 40%) and 2 : 3-dimethyl-2 : 3-diphenylbutane (1·6 g., 17%). The induction period was 5 min.

(iii) At 95°. *n*-Butyl bromide (5·35 g., 0·039 mole), *n*-butyl-lithium (0·0376 mole), and *iso*propylbenzene (36 g.) gave, after 18 hr., butane (19·5%), butene (3·5%), *n*-octane (2·1 g., 43%), 2 : 3-dimethyl-2 : 3-diphenylbutane (1·6 g., 18%), and lithium hydride (9%). This last was evidently derived from thermal decomposition of *n*-butyl-lithium.[15] In addition, a colourless liquid, b. p. 220—255° (*ca.* 0·5 g.), was obtained, which may have been a mixture of *n*-butyl*iso*propylbenzenes. The induction period was ½ min.

(g) n-*Butyl iodide and* n-*butyl-lithium.* (i) At 95°. *n*-Butyl iodide (7·2 g., 0·039 mole) was added during 10 min. to *n*-butyl-lithium (0·0376 mole) in *iso*propylbenzene (36 g.). There was an instant precipitate of lithium iodide and the mildly exothermic reaction was 91% complete after 70 min. After addition of water, *n*-octane (1·45 g., 35%) and 2 : 3-dimethyl-2 : 3-diphenylbutane (1·15 g., 14%) were obtained, together with liquid fractions with the following b. p.s : (i) <245° (0·2 g.), (ii) 245—255° (1·9 g.), (iii) 255—280° (0·2 g.); and a pale yellow residue (0·3 g.) : fractions (i)—(iii) were moderately unsaturated to bromine in carbon tetrachloride. Fraction (ii) would correspond to *n*-butyl*iso*propylbenzenes, but the analysis indicated two fewer hydrogen atoms per molecule (Found : C, 89·75; H, 10·2. Calc. for $C_{13}H_{20}$: C, 88·6; H, 11·4. Calc. for $C_{13}H_{18}$: C, 89·6; H, 10·4%). Oxidation of the hydrocarbon (0·1931 g.) with chromium trioxide (2·1 g.) in acetic acid (3 ml.) at 130° for 24 hr. gave terephthalic acid (0·0116 g.) (dimethyl ester, m. p. and mixed m. p. 141°) and benzoic acid (0·0187 g.), m. p. 120° and mixed m. p. 120—121°. *iso*Phthalic acid was shown to be absent by the test with thallous acetate.[20]

In a duplicate experiment, the yield of 2 : 3-dimethyl-2 : 3-diphenylbutane was 15%.

(ii) At 60°. *n*-Butyl iodide (7·8 g., 0·0425 mole), added during 30 min. to *n*-butyl-lithium (0·045 mole) in *iso*propylbenzene (39 g.), gave, after a further 2½ hr. at 60°, 2 : 3-dimethyl-2 : 3-diphenylbutane (0·9 g., 9·5%). Other products were not investigated. The induction period was ½ min.

(h) sec.-*Butyl bromide and* sec.-*butyl-lithium at* 95°. *sec.*-Butyl bromide (5·6 g., 0·041 mole) was added during 30 min. to *sec.*-butyl-lithium (0·039 mole) in *iso*propylbenzene (37·5 g.). There was an immediate exothermic reaction. Unexpectedly, the evolution of gas almost ceased after the addition of little more than half of the halide. After 5 hr. at 95°, the titres of hydrolysed 1-ml. portions of the supernatant liquid and the stirred suspension were 0·78 ml. and 1·40 ml. of 0·2*N*-hydrochloric acid respectively : after a further 18 hr. the corresponding titres were 0·47 and 1·35 ml. A test with Michler's ketone [19] on a sample of the stirred suspension was negative : a control test with *sec.*-butyl-lithium was strongly positive. These facts suggest that lithium hydride may have been formed. After the addition of water, 2 : 3-dimethyl-2 : 3-diphenylbutane (0·55 g., 6%) was obtained, together with *ca.* 1 g. of an unidentified liquid, b. p. 110—150°/8 mm.

(i) n-*Butyl iodide and* n-*butylsodium at* 25°. *n*-Butylsodium was prepared by the addition of di-*n*-butylmercury (10·0 g., 0·0318 mole) to sodium (1·47 g., 0·064 g.-atom) in *n*-pentane (30 ml.). After 24 hr., *n*-pentane was removed under reduced pressure, and the solid residue was kept under 0·05 mm. pressure for 5 min. before addition of *iso*propylbenzene (60 g.) and, during 1 hr., of *n*-butyl iodide (12·9 g., 0·07 mole). After 1 hr. more of stirring at 20—25°, butane (27%) and butene (10%) were pumped off. The reaction product was filtered under nitrogen without treatment with water. The material of b. p. >160° (0·2 g.) partly

[20] Bryce-Smith, *Chem. and Ind.*, 1953, 244.

crystallised on long storage. Recrystallisation gave 2 : 3-dimethyl-2 : 3-diphenylbutane (0·050 g., 0·4%).

(j) *Reaction of* n-*butyl-lithium with iodine.* Dry, finely powdered iodine (5·2 g., 0·0205 mole) was added in 30 min. from a gas-tight hopper to *n*-butyl-lithium (0·0405 mole) in *iso*propylbenzene (39 g.) at 60°. The colourless product was kept at this temperature for a further 18 hr. After filtration from lithium iodide, fractional distillation gave a fraction, b. p. 125—145°, which was shown to contain *n*-butyl iodide by the formation of *S*-*n*-butylthiuronium picrate (0·5 g.), m. p. and mixed m. p. 176—177°. Addition of methanol containing a little ethanol to the material of b. p. >160° gave 2 : 3-dimethyl-2 : 3-diphenylbutane (0·5 g., 10%). Cf. experiment (g)(ii).

(k) *Reaction of* n-*butyl-lithium with* n-*butyl bromide in benzene.* *n*-Butyl bromide (5·35 g., 0·039 mole) was added in 30 min. to a refluxing solution of *n*-butyl-lithium (0·0376 mole) in benzene (40 ml.). The mixture was heated under reflux for a further 6 hr., cooled, and treated with water. Fractional distillation of the dried organic layer gave fractions with the following b. p.s : (i) 110—175° (0·3 g.), (ii) 175—185° (0·1 g.), (iii) 185—240° (0·3 g.); and an oily residue (1 g.). Infrared spectra of (i)—(iii) closely resembled the spectrum of pure *n*-butylbenzene (kindly taken by Mr. R. J. D. Smith), except that the overall transmissions were greater. This suggested that *n*-butylbenzene was present in admixture with material relatively transparent over the range examined (4—15 μ). Control experiments showed that as little as 10% of diphenyl in the mixture would have been detected had it been present.

Butane (1·2 g., 28%) and butene (0·5 g., 12%) were evolved during the reaction.

To investigate the possibility that *n*-butylbenzene was produced by a direct reaction between *n*-butyl-lithium and benzene, a solution of *n*-butyl-lithium (0·085 mole) in benzene (50 ml.) was heated under reflux for 7 days. The gas evolved (2·3 g.) was a mixture of butane (16%) and butene (84%). No trace of *n*-butylbenzene was detected, and the main reaction was evidently a thermal decomposition which did not involve the solvent (cf. Part V [15]).

Discussion

Some of the present results are summarised in the Table.

Yields (%) of products from the reactions of halides with alkali metals and alkali-metal alkyls.

Halide	Metal reagent	Temp.	"Dicumyl" *	Octane	Butane	Butene	Butane : butene
n-C_4H_9I	Li	95°	19	35			
,,	,,	130	17	24	20	10	2·0
,,	Na	25	0·0	83	1·6	1·4	1·15
,,	,,	130	1·2	61	10·5	3·5	3·0
,,	K	130	0·02	29			3·0
n-C_4H_9Cl	*n*-C_4H_9Li	95	12	29			
n-C_4H_9Br	,,	95	18	43	19·5	3·5	5·6
n-C_4H_9I	,,	95	14	35			
n-C_4H_9Br	,,	25	9	50			
n-C_4H_9I	,,	60	9·5				
n-C_4H_9Br	,,	60	17	40			
sec.-C_4H_9Br	*sec.*-C_4H_9Li	95	6				1·5
n-C_4H_9I	*n*-C_4H_9Na	25	0·4		27	10	2·7
I_2	*n*-C_4H_9Li	60	10				

* 2 : 3-Dimethyl-2 : 3-diphenylbutane. Blank spaces in the Table indicate that no measurement was made.

It is considered that the production of 2 : 3-dimethyl-2 : 3-diphenylbutane in these various reactions indicates that free butyl radicals are formed, and that they abstract hydrogen from the solvent as follows :

$$C_4H_9\cdot + C_6H_5\cdot CHMe_2 \longrightarrow C_4H_{10} + C_6H_5\cdot CMe_2\cdot$$
$$2C_6H_5\cdot CMe_2\cdot \longrightarrow C_6H_5\cdot CMe_2\cdot CMe_2\cdot C_6H_5$$

In Part V [15] of this Series, *n*-butyl radicals which were generated by photolysis of (*a*) di-*n*-butylmercury and (*b*) a mixture of *n*-butyl iodide and silver were shown to react with *iso*propylbenzene in the above manner. Moreover, it has been shown that the decomposition of *n*-butyl-lithium [15] and of sodium and potassium alkyls [16] in *iso*propylbenzene produces no 2 : 3-dimethyl-2 : 3-diphenylbutane. Neither the alkali metals used

nor the alkyl halides react with *iso*propylbenzene under the conditions of the present experiments.

Particular attention may be drawn to the following points. (*a*) The yields of 2 : 3-dimethyl-2 : 3-diphenylbutane from the reactions between alkali metals and *n*-butyl iodide under corresponding conditions decreased in the order lithium > sodium > potassium. (*b*) With sodium, a little 2 : 3-dimethyl-2 : 3-diphenylbutane was formed at 130°, but none at 25°. (*c*) The reaction between *n*-butyl iodide and lithium at 95° gave a yield of 2 : 3-dimethyl-2 : 3-diphenylbutane per *n*-butyl group only slightly greater than that from the corresponding reaction between *n*-butyl iodide and *n*-butyl-lithium. (*d*) The reaction between *n*-butyl-lithium (2 mol.) and iodine (1 mol.) gave a yield of 2 : 3-dimethyl-2 : 3-diphenylbutane per *n*-butyl group almost identical with that from the corresponding reaction between equimolecular proportions of *n*-butyl-lithium and *n*-butyl iodide.

On the assumption (which is further discussed below) that, at a particular temperature, the yields of 2 : 3-dimethyl-2 : 3-diphenylbutane from the present reactions are related to the numbers of free *n*-butyl radicals which are formed, it is concluded from (*a*) that the order lithium > sodium > potassium is the order of decreasing tendency to produce these radicals. From (*c*) it is evident that the free radicals formed in the "lithium-Wurtz" reaction are very largely derived from a new type of homolytic reaction between alkyl-lithium compound and alkyl halide, rather than from a ***direct*** reaction between lithium and alkyl halide. This is a point of difference between Wurtz-type reactions in solution and the corresponding gas-phase reactions [1] and may be due to the fact that Wurtz reactions involve bulk metal, whereas the gas-phase reactions involve free metal atoms under conditions of low pressure and relatively high temperature where the possibility of capture of a free alkyl radical by a metal atom is much less. However, in the present reactions with *n*-butyl iodide, the fact that lithium appeared to give a slightly higher yield of 2 : 3-dimethyl-2 : 3-diphenylbutane than did *n*-butyl-lithium may indicate that a few additional free *n*-butyl radicals were formed in the former case by a direct reaction between the halide and the metal; but the difference in yields is too small to justify a definite conclusion. Identical yields of octane were obtained from these two experiments.

From (*d*), it appears that the initial reaction between *n*-butyl-lithium and iodine is : $n\text{-}C_4H_9Li + I_2 \longrightarrow n\text{-}C_4H_9I + LiI$. *n*-Butyl iodide may then react with a further mol. of *n*-butyl-lithium to produce free *n*-butyl radicals and other products. The hypothetical reaction, $n\text{-}C_4H_9Li + \frac{1}{2}I_2 \longrightarrow n\text{-}C_4H_9^{\bullet} + LiI$, seems not to occur under the present conditions.

In the Wurtz reactions with sodium or potassium at 130°, analogy with the lithium reactions suggests that the very limited formation of free radicals arises from a homolytic reaction between alkyl-sodium or -potassium compound and alkyl halide. The mechanism could not be tested because alkyl-sodium and -potassium compounds are thermally unstable at 130° and would also rapidly metallate *iso*propylbenzene. These difficulties are less important at 25°, at which *n*-butyl iodide and sodium gave no indication of the formation of free radicals. The production of a trace of 2 : 3-dimethyl-2 : 3-diphenylbutane from a reaction between *n*-butyl iodide and *n*-butylsodium in *iso*propylbenzene at 25° was therefore unexpected. The anomaly may possibly arise from the unavoidable presence of mercury in the reaction mixture, and the result does not seriously affect the conclusion that no significant numbers of free *n*-butyl radicals were formed during the reactions between *n*-butyl iodide and sodium at 25°. The blue colour of the reaction mixture at 25° was rapidly discharged at 130°, but there was no detectable liberation of free radicals during this process. The colour may result from lattice defects in the sodium iodide crystals, possibly associated with a stoicheiometric excess of sodium atoms, although its temperature stability was rather lower than expected.[21]

In all the cases where measurement was made, more butane than butene was formed, and the yields of butane exceeded the yields of 2 : 3-dimethyl-2 : 3-diphenylbutane. Both

[21] Burns and Williams, *Nature*, 1955, **175**, 1043; Scott, Hrostowski and Bupp, *Phys. Rev.*, 1950, **79**, 341, 346.

the disproportionation of free *n*-butyl radicals and a heterolytic elimination reaction between butyl halide and metal butyl should produce butane and butene in equal amounts. The observed preponderance of butane is superficially in accord with the belief that free butyl radicals abstract hydrogen from the solvent, but the probability of side reactions, *e.g.*, n-$C_4H_9Li + CH_3{\cdot}CH_2{\cdot}CH{:}CH_2 \longrightarrow n$-$C_4H_{10} + CH_3{\cdot}CHLi{\cdot}CH{:}CH_2$, and n-$C_4H_9Li \longrightarrow n$-$C_4H_8 + LiH$, blurs the significance of the butane : butene ratios.

It is next necessary to consider the quantitative significance of the yields of 2 : 3-dimethyl-2 : 3-diphenylbutane. First, it may be concluded from Kharasch, McBay, and Urry's results [22] that the dimerisation of αα-dimethylbenzyl radicals can occur almost quantitatively. These radicals have little or no tendency to disproportionate. Some combination of *n*-butyl and αα-dimethylbenzyl radicals to give 2-methyl-2-phenylhexane may have occurred under the present conditions; but this hydrocarbon would also have resulted from a reaction between *n*-butyl halide and α-metallated *iso*propylbenzene.

A further question is whether the butyl radicals reacted with the solvent to produce an equal number of αα-dimethylbenzyl radicals. Two factors are important here : (*a*) the extent to which free butyl radicals dimerise and disproportionate under the present conditions, and (*b*) the possibility of a " cage effect " following the reaction, BuM + BuX $\longrightarrow$ 2Bu· + MX (M = Li, Na, or K; X = Cl, Br or I).

Considering, first, under (*a*) those butyl radicals which were truly " free " in that they had escaped from any solvent cage, it is probable that at least 50% of them abstracted hydrogen from the solvent. This seems to follow from a result described in Part V [15] where the photolysis of di-*n*-butylmercury in *iso*propylbenzene gave a 47% yield of 2 : 3-dimethyl-2 : 3-diphenylbutane and 2% of octane, together with unidentified material.

The importance of a " cage effect " is less easy to assess. The above considerations suggest that even the highest yields, *ca.* 20%, of 2 : 3-dimethyl-2 : 3-diphenylbutane correspond to the appearance of only *ca.* 40% of the butyl groups in the reagents as free butyl radicals. From the form of the reactions, it seems highly probable that butyl radicals are liberated in pairs : and if this is so, at the instant when such a pair is liberated by (say) the interaction of *n*-butyl bromide and *n*-butyl-lithium, the local concentration of *n*-butyl radicals must be greater than the mean concentration over the solution as a whole. Primary dimerisation and primary disproportionation will then be favoured until the radicals have diffused well apart, *i.e.*, have become truly " free," or have reacted with the solvent. However, the possibility that a " cage effect " operates to produce the *bulk* of the usual products of Wurtz reactions is excluded with reasonable certainty because in disproportionation reactions between an alkylsodium compound RNa and an alkyl halide R'X, the greater part of the saturated hydrocarbon is derived from R, and the unsaturated hydrocarbon from R'.[6, 14b] Also, there seems to be no obvious reason why radicals should be so much more effectively " caged " in the reactions of alkyl halides with RNa or RK compounds than in the corresponding reactions with RLi compounds.

(1) n-$C_4H_9I + 2M \longrightarrow n$-$C_4H_9M + MI$

(2) n-$C_4H_9M + n$-$C_4H_9I \longrightarrow 2n$-$C_4H_9{\cdot} + MI$

(3) $2n$-$C_4H_9{\cdot} \longrightarrow n$-$C_8H_{18}$ (primary and secondary dimerisation)

$2n$-$C_4H_9{\cdot} \longrightarrow n$-$C_4H_{10} + n$-$C_4H_8$ (primary and secondary disproportionation)

(4) n-$C_4H_9{\cdot}$ + Solvent * $\longrightarrow n$-C_4H_{10} + Radicals derived from solvent

(5) n-$C_4H_9M + n$-$C_4H_9I \longrightarrow n$-$C_8H_{18}$ + MI (heterolytic)

(6) n-$C_4H_9M + n$-$C_4H_9I \longrightarrow n$-$C_4H_{10} + n$-$C_4H_8$ + MI (heterolytic)

* It is normal practice to employ diethyl ether as a solvent in Wurtz reactions. From the results of Kharasch and Urry,[22] it appears that diethyl ether is a rather more efficient trap for alkyl radicals than is *iso*propylbenzene, although the reaction products are less characteristic. Any radicals which might be formed during a Wurtz reaction in diethyl ether would therefore have an even smaller chance to dimerise and disproportionate.

[22] Kharasch, McBay, and Urry, *J. Org. Chem.*, 1945, **10**, 401.

These considerations lead the writer to conclude that, in the Wurtz reactions which have now been studied, the usual coupling and disproportionation products are formed mainly by heterolytic reactions between metal alkyl and alkyl halide, and that the homolytic reaction with which these compete is only appreciable in extent when lithium is used. This view of the Wurtz reaction is expressed, for *n*-butyl iodide, in the equations (1)—(6) (M = Li, Na or K).

Further minor side reactions can include : (7) $n\text{-}C_4H_9M \longrightarrow n\text{-}C_4H_8 + MH$; metallation of butene from reactions (3), (6), and (7) by $n\text{-}C_4H_9M$; and attack on the solvent by $n\text{-}C_4H_9M$.

Coupling and disproportionation reactions between alkali-metal alkyls and alkyl halides have been widely investigated.[14] The results have been interpreted in terms of heterolytic reactions in which the rate-determining step may vary from case to case : [14c,e] the possibility of prior co-ordination between alkali-metal cation and halogen has been suggested. The possibility of a homolytic mechanism has been discussed by Morton and Cluff [13] without direct experimental evidence*. The present results partially accord with their " radical-pair " hypothesis.†

The idea of competing homolytic and heterolytic reactions between two molecular species in the same environment implies that the corresponding transition states or complexes have comparable energies. The orientation of any two molecules at the moment of collision may, in part, decide which reaction path is followed. One might expect that free radicals would be most readily produced in straight-line collisions, *e.g.*, R–Li→←Br–R, where interaction between the alkyl groups is at a minimum. Also, loose co-ordination between metal and halogen might be a preliminary to homolysis of the R–Li and R–Br bonds. The induction period before precipitation of lithium halide may be significant in connection with the last suggestion.

The reactions between lithium or alkyl-lithium compounds and alkyl halides may have some practical value as sources of free alkyl radicals in solution. They have the merit of giving only one radical species at a time. Thus, when *n*-butyl radicals were generated in benzene from *n*-butyl bromide and *n*-butyl-lithium, the main products appeared to be aliphatic hydrocarbons which could not be separated; but infrared data indicated that a little *n*-butylbenzene was formed. No diphenyl was detected. The absence of solvent dimer is here not surprising in view of the relatively low reactivity of benzene towards many free radicals. It is also evident that *n*-butyl radicals add to benzene much less readily than do phenyl radicals.

The present investigations are being extended to the Fittig reaction, and to the use of metals outside Group I.

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* Kharasch and Urry [23] showed that free radicals are formed during the reactions between certain alkyl halides and alkylmagnesium bromides. They originally proposed a chain mechanism involving magnesium sub-bromide; but Kharasch and Reinmuth [24] have more recently given an alternative explanation that a direct homolytic reaction can occur, *viz.*, $RMgX + RX \longrightarrow 2R\cdot + MgX_2$. This suggestion appears very attractive in the light of the present results, where the question of catalysis by metal subhalide does not arise.

† Morton's further applications of this hypothesis to thermal decomposition [13] and metallation reactions [25] of alkali-metal alkyls seem to be contradicted by the published evidence.[15, 16, 26]

[23] Kharasch and Urry, *J. Org. Chem.*, 1948, **13**, 101.
[24] Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, 1954, p. 131.
[25] Morton, Claff, and Collins, *J. Org. Chem.*, 1955, **20**, 428; Morton and Claff, *ibid.*, p. 981.
[26] Bryce-Smith, Gold, and Satchell, *J.*, 1954, 2743; Gronowitz, *Arkiv Kemi*, 1954, **7**, 361; Gronowitz and Halvarson, *ibid.*, 1955, **8**, 343; Hall, Piccolini, and Roberts, *J. Amer. Chem. Soc.*, 1955, **77**, 4540.

319. *Fatty Acids. Part IV.* The Preparation of Eight 9 : 10 : 12 : 13-Tetrahydroxystearic Acids.†*

By K. E. Bharucha and F. D. Gunstone.

Naturally occurring epoxyoleic acid is proved to be an optically active *cis*-epoxide. It has been converted into *threo*- and *erythro*-12 : 13-dihydroxyoleic acid and, from these, eight optically active 9 : 10 : 12 : 13-tetrahydroxystearic acids have been prepared.

The relations between oleic and elaidic acid, the two racemic 9 : 10-dihydroxystearic acids derived from them, and various intermediates used in their preparation have now been made clear by Swern [1] who, using knowledge gained by several investigators, has been able to rationalise the stereochemistry of the processes involved. This work has opened the way to a similar explanation of the relation between linoleic acid (octadeca-*cis*-9 : *cis*-12-dienoic acid), its configurational isomers, and the tetrahydroxystearic acids derived from them. Although Swern's work removes certain theoretical difficulties concerning the relation between the tetrahydroxystearic acids and the dienoic acids, there remain several practical difficulties including that of obtaining pure linoleic acid, the fact that oxidation of linoleic acid or of its all-*trans*-isomer (linelaidic acid) always gives a mixture of two racemates separable only with difficulty and frequently giving eutectic mixtures, and the fact that direct oxidation of linoleic or linelaidic acids can give only four of the eight possible racemates so that indirect methods are required to obtain the other four racemates.

It is now accepted that linoleic acid present in seed oils is entirely the *cis-cis*-isomer,[2] that linelaidic acid is the *trans-trans*-isomer,[2] that oxidation by dilute alkaline permanganate involves *cis*-addition of hydroxyl groups to the double bond,[1] and that reaction with peracids or hydroxylation proceeding through the halogenohydrins is equivalent to *trans*-addition of hydroxyl groups.[1] The terms *cis* and *trans* used by several investigators to describe the resulting glycols are both confusing and incorrect when applied to open-chain compounds and should be replaced by *threo*- and *erythro*-. By definition *threo*-compounds result by *trans*-addition to a *cis*- or by *cis*-addition to a *trans*-ethylenic compound, whilst the *erythro*-isomers are the products of *cis*-addition to a *cis*- or *trans*-addition to a *trans*-ethylenic compound. 9 : 10 : 12 : 13-Tetrahydroxy stearic acid containing four asymmetric centres should exist in sixteen optically active forms and eight racemates. Eight stereoisomers are shown below (I—VIII), the other eight being represented by their enantiomorphs. These are obviously grouped in four pairs. It follows that *cis*-oxidation (dilute alkaline permanganate) of linoleic acid affords the two di-*erythro*-isomers which should also result from *trans*-oxidation of linelaidic acid; similarly the two di-*threo*-forms are produced from linoleic acid by *trans*-addition (performic acid) or from linelaidic acid by *cis*-addition, but the mixed *threo-erythro*-isomers (III—VI) cannot be produced directly from linoleic or linelaidic acids. In Table 1 the results obtained by several investigators are listed, the configuration of the products being determined on the basis of present views. The general agreement is immediately obvious.

Reference to the mixed *threo-erythro*-isomers is confined to reports by Kass and Burr [10] and by McKay and Bader.[13] The last authors claim to have prepared all eight racemic forms but owing to the known difficulties of working with these compounds we tried to prepare the eight racemates by an alternative procedure. We now report the preparation of eight tetrahydroxystearic acids which we consider to be optically active.

The starting materials for our oxidation experiments were the *threo*- and the *erythro*-form of 12 : 13-dihydroxyoleic acid which we obtained from 12 : 13-epoxyoleic acid (IX)

* Part III, *J.*, 1955, 3782.
† Geneva numbering, $CO_2H = 1$.

[1] Swern, *J. Amer. Chem. Soc.*, 1948, **70**, 1235.
[2] Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433.

TABLE 1. *Di*-erythro- *and di*-threo-*tetrahydroxystearic acids.*

Date	Investigator	Reactant C_{18} acid	Reagent	M.p.s of di-*erythro*-acids		M.p.s of di-*threo*-acids	
1887	Hazura [3]	Linoleic *	$KMnO_4$	173°			
1909	Rollett [6]	,,	,,	171—173			
1912	Meyer and Beer [5]	,,	,,	173	162—163°		
1922	Nicolet and Cox [4]	,,	,,	170	153		
	,, ,,	,,	Hydrol. of halogeno-hydrin	—	—	144°	135°
1932	Smith and Chibnall [7]	,,	$KMnO_4$	172	159—160	—	—
1935	Green and Hilditch [9]	,,	,,	173	155	—	—
	,, ,,	,,	$AcOH–H_2O_2$	—	—	146	126
1937	Birosel [9]	,,	$KMnO_4$	174	164	—	—
1939	Kass and Burr [10]	Linelaidic	,,	—	—	146	122
1939	Riemenschneider *et al.* [11]	Linoleic	,,	174	163·5	—	—
1939	Hilditch and Jasperson [12]	,,	,,	173	157	—	—
	,, ,,	Linelaidic	,,	—	—	144	135
1948	McKay and Bader [13]	*erythro*-9 : 10-Dihydroxy-*cis*-12-en	,,	174	164	—	—
	,, ,,	*threo*-9 : 10-Diacetoxy-*cis*-12-en	$H·CO_2H–H_2O_2$	—	—	148	126
1954	McKay *et al.* [14]	Linoleic acid	,,	—	—	148	126
1956	Present work †	*erythro*-12 : 13-Dihydroxyoleic	$KMnO_4$	177	156	—	—
		threo-12 : 13-Diacetoxyoleic	$H·CO_2H–H_2O_2$	—	—	148	122

* The linoleic acid is either debrominated tetrabromostearic acid or a concentrate of oleic and linoleic acid prepared from a seed oil containing high proportions of the latter.

† The products obtained here are optically active (see text) whilst all the others are racemates.

TABLE 2. *Specific rotation.*

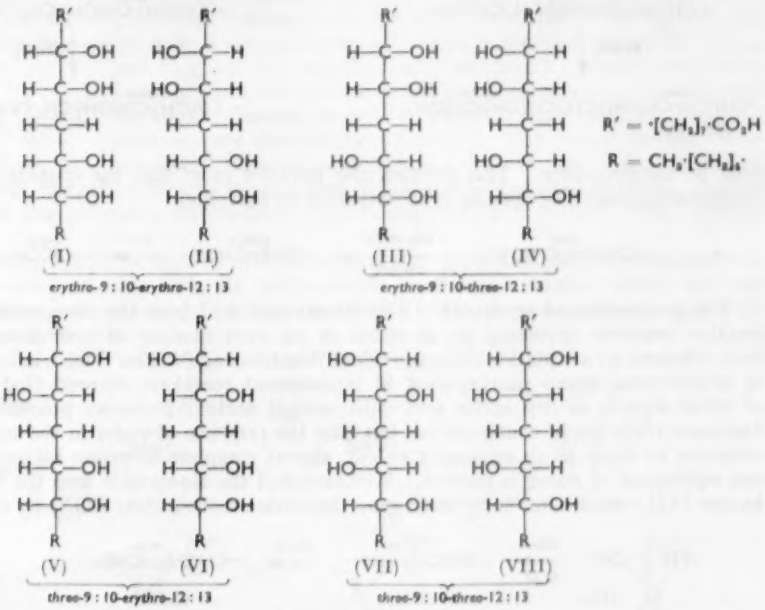
Acid	M. p.	Solvent: AcOH	Solvent: EtOH	M. p. of Me ester	Solvent: AcOH	Solvent: EtOH
threo-12 : 13-Dihydroxyoleic		**−6·8°** (19°, −0·69°)	**−5·7°** (19°, −0·51°)		—	—
erythro- ,, ...		**+1·2** (20, +0·12)	**−3·6** (20, −0·29)		—	—
threo-12 : 13-Dihydroxystearic.....		+1 (15·5, +0·01)	**−1·3** (20, −0·05)		—	—
erythro- ,, ...		+3 (16·5, +0·02)	**−1·7** (20·5, −0·03)		—	—
Tetrahydroxystearic acids :						
threo-9 : 10-*threo*-12 : 13-	148°	—	—		—	—
,, ,, ...	122	**−9** (17, −0·04)	0		0°	0°
erythro-9 : 10-*threo*-12 : 13-	165	−6 (20, −0·01)	—	136°	0	−1 (19, −0·01°)
,, ,, ...	112	—	—	—	—	—
threo-9 : 10-*erythro*-12 : 13-	156	**−44** (18·5, −0·35)	**−7** (20, −0·03)	145	**−46** (18·5°, −0·09°)	—
,, ,, ...	130	**+14** (17, +0·10)	**+5** (20, +0·03)	114	**+17** (20, +0·12)	**+22** (20, +0·08)
erythro-9 : 10-*erythro*-12 : 13-	177	**−10** (18·5, −0·04)	**+6** (20, +0·01)	171	**−16** (18·5, −0·08)	**+22** (20, +0·05)
,, ,, ...	156	+14 (17, +0·02)	0	145	0	−2 (19, −0·01)
			Cephalocroton cordofanus seed oil		**+3·4** (16·5, +0·08)	—

Measurements were made with a 2 dm. tube and sodium light.

A dash (—) indicates that no measurement was made, 0 indicates a zero value.

Values in heavy type are calculated from observed rotations of 0·03° or greater (some inactive dihydroxy- and tetrahydroxy-stearic acids gave observed rotations of only 0·00° or 0·01°); figures in parentheses are temperature and the observed rotation.

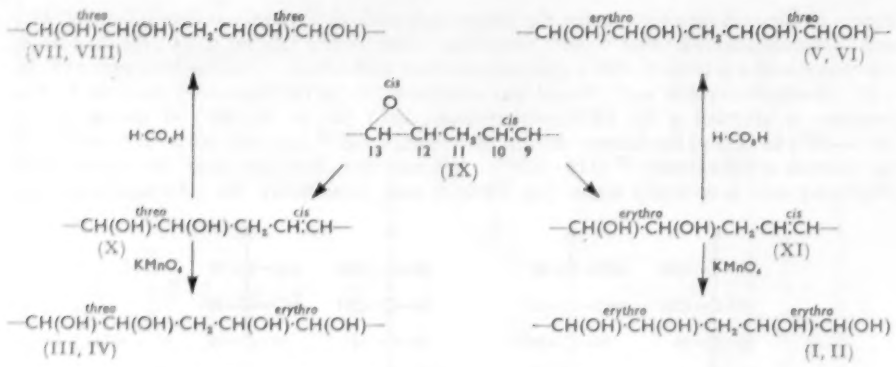
known to occur in quantity among the component acids of *Vernonia anthelmintica* [15] (74%) and *Cephalocroton cordofanus* [16] (66%) seed oils. One isomer (X), m. p. 54°, resulted when the epoxy-acid was treated with acetic acid and then with alkali. This has been proved to be a 12 : 13-dihydroxyoleic acid [15a] and was considered to be the *threo*-form since on hydrogenation it afforded a 12 : 13-dihydroxystearic acid (m. p. 95—96°) of similar m. p. (96·5—97°) to that of the known racemic *threo*-compound [17] and very different from that of the racemic *erythro*-isomer [17] (119—120°). We now find, however, that the unsaturated dihydroxy-acid is optically active (see Table 2) and, presumably, the saturated acid also,



despite the low observed rotation; the identity of melting point between the racemic *threo*- and our dihydroxyoleic acid is thus inadequate proof of the *threo*-configuration of the latter and we now offer independent proof of this by the partial synthesis from it of octadec-*trans*-12-enoic acid.

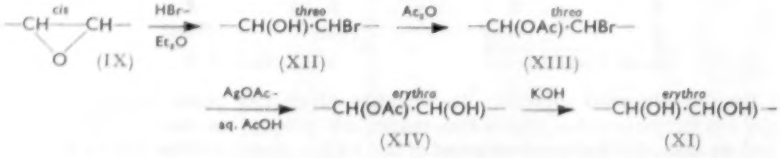
The dihydroxyoleic acid (X), when converted into the dibromide by Bowman's procedure [18] and subsequently debrominated, gave octadec-*trans*-12-enoic acid. This is quite certain since the melting point of this acid and of the two dihydroxystearic acids obtained from it agree with those expected of the *trans*-acid. Since the bromination occurs with inversion and debromination is a *trans*-elimination the dihydroxy-compound

[3] Hazura, *Monatsh.*, 1887, **8**, 147; 1888, **9**, 180.
[4] Rollett, *Z. physiol. chem.*, 1909, **62**, 410.
[5] Meyer and Beer, *Monatsh.*, 1912, **33**, 311.
[6] Nicolet and Cox, *J. Amer. Chem. Soc.*, 1922, **44**, 144.
[7] Smith and Chibnall, *Biochem. J.*, 1932, **26**, 218.
[8] Green and Hilditch, *ibid.*, 1935, **29**, 1552.
[9] Birosel, *J. Amer. Chem. Soc.*, 1937, **59**, 689.
[10] Kass and Burr, *ibid.*, 1939, **61**, 1062.
[11] Riemenschneider, Wheeler, and Sando, *J. Biol. Chem.*, 1939, **127**, 391.
[12] Hilditch and Jasperson, *J. Soc. Chem. Ind.*, 1939, **58**, 233.
[13] McKay and Bader, *J. Org. Chem.*, 1948, **13**, 75.
[14] McKay, Levitin, and Jones, *J. Amer. Chem. Soc.*, 1954, **76**, 2383.
[15] (*a*) Gunstone, *J.*, 1954, 1611; (*b*) Bharucha and Gunstone, *J. Sci. Food Agric.*, 1955, **6**, 373.
[16] Bharucha and Gunstone, unpublished observation.
[17] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.
[18] Ames and Bowman, *J.*, 1951, 1079.



must be the *threo*-form. This reaction also provides proof that the epoxide has the *cis*-configuration since ring opening is accompanied by inversion.[1]

The preparation of *erythro*-12 : 13-dihydroxyoleic acid from the *cis*-epoxide requires a reaction sequence involving no inversion or an even number of inversions. This has been achieved by adaptation of some work of Winstein and Buckles [19] who, in investigations of neighbouring-group participation in replacement reactions, showed that interaction of silver acetate in dry acetic acid with several acetoxy-bromides proceeds with predominant retention of configuration, but that the presence of water in the solvent causes inversion to occur to an increasing extent, almost complete inversion taking place when one equivalent of water is present. We converted the *cis*-epoxide into the *threo*-bromohydrin (XII) which after acetylation gave the *erythro*-monoacetate (XIV) by reaction with



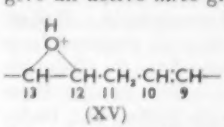
silver acetate in wet acetic acid, and this on hydrolysis afforded the required *erythro*-glycol (XI). The high overall yield of glycol resulting from this four-stage process (78% crude, 69% pure)—which also involves in the final stage removal of the other acids originally present in the oil—and the ease with which the glycol is obtained pure are evidence of the high stereospecificity of these reactions. We have simplified the procedure of Winstein and Buckles by reducing the reaction period with silver acetate from 8 to 2 hours and by effecting the reaction with silver nitrate in wet alcohol (cf. Bevan, Malkin, and Smith [20]).

The *erythro*-dihydroxyoleic acid was a crystalline solid with m. p. (88°) greater than that of the *threo*-isomer (54°), like many similar compounds. Hydrogenation gave *erythro*-12 : 13-dihydroxystearic acid with a higher m. p. (126°) than that (119—120°) previously recorded for the racemic isomer.[17] This difference is due to the fact that our compound is optically active; the observed rotation is very small, but it is larger for its unsaturated precursor. The structures of the saturated and the unsaturated *erythro*-dihydroxy-acid were confirmed by oxidation.

Before considering how far the optical activity of these dihydroxy-acids is to be expected it is necessary to remark that optical activity of long-chain compounds is

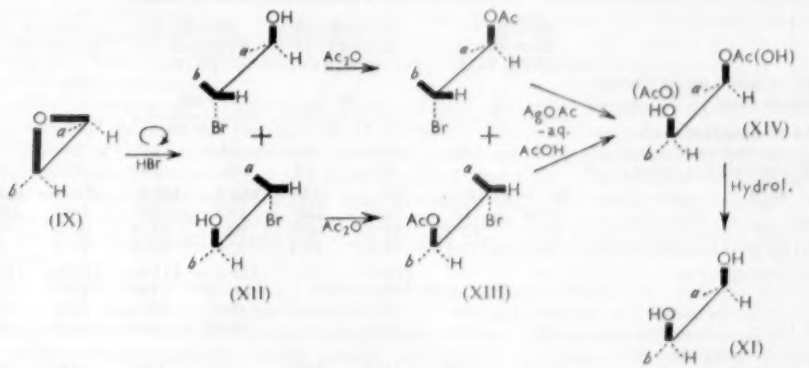
[19] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787.
[20] Bevan, Malkin, and Smith, *J.*, 1955, 1043.

frequently so small that it cannot be measured and in the present instance this difficulty was sometimes increased by low solubilities (Baer and Fischer [21] showed that certain triglycerides which should be optically active lack observable rotatory power but are optically active when one or more of the usual aliphatic acyl groups is replaced by an aromatic acyl group). Epoxyoleic acid contains two asymmetric centres and the naturally occurring acid may be expected to be an enantiomorphic form and indeed must be if it is to give rise to optically active derivatives. We have now observed a small dextrorotation with *Cephalocroton cordofanus* seed oil. Consideration of the reaction mechanism involved in the preparation of the *erythro*-dihydroxyoleic acid suggests that an optically active epoxide should give an active glycol (see scheme). On the other hand, the active epoxide will give an active *threo*-glycol only if the conjugate acid (XV) is attacked unequally at $C_{(12)}$ and $C_{(13)}$ by the acetate ion: an attack equally distributed between these two centres would give a racemic glycol. Although the specific rotation of these two acids is fairly small the observed rotations are definite (see Table 2). The values for the corresponding saturated acids are less definite, but as hydrogenation does not affect the active centres racemisation would not be expected to occur; further the m. p. of the saturated *erythro*-isomer differs appreciably from that of the racemic compound.



(XV)

The two dihydroxyoleic acids have been oxidised with dilute alkaline potassium permanganate and with performic acid. In each case the product is a mixture which has been separated by an extensive series of crystallisations. Some general comments are made before discussing the results.



a = $CH_3 \cdot [CH_2]_4 \cdot$ b = $\cdot CH_2 CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$

(i) In the performic acid oxidation of *threo*-dihydroxyoleic acid the main product was a low-melting, ether-soluble compound which accompanied the desired tetrahydroxyacids. Two individual compounds were isolated from this product (m. p.s 77·5—78°, 94—95°) but these were not identified. Similar products have been isolated by other investigators,[5,14] whilst Paul and Tchelitcheff [22] have reported that furan compounds are formed in the hydrolysis of 1 : 2 : 4 : 5-diepoxypentane. We found little or none of these products when we oxidised diacetoxyoleic acid and this became our standard procedure.

(ii) The separation of the two products obtained in each reaction involves many crystallisations. The higher-melting isomer being the less soluble is generally the more easily isolated; purification of the lower-melting isomer was more difficult and we are less confident of the homogeneity of the latter though in all cases the products were crystallised to constant melting point.

[21] Baer and Fischer, *Chem. Rev.*, 1941, **29**, 287.
[22] Paul and Tchelitcheff, *Compt. rend.*, 1954, **239**, 1504.

(iii) McKay and his colleagues [14] report that the two tetrahydroxy-acids are more easily separated as their methyl esters and in some cases we have checked our results by separation of both acids and esters with subsequent hydrolysis of the separated esters.

(iv) We emphasise the purity of our starting materials. Both 12 : 13-dihydroxyoleic acids are crystalline solids, readily purified and available in quantity from the sources already mentioned. This is in contrast to much of the previous work on this problem which has been undertaken with impure starting materials. Many investigators have used a concentrate of linoleic acid obtained from a suitable source and containing appreciable quantities of oleic acid. Alternatively, linoleic acid has been prepared by debromination of tetrabromostearic acid and is known then to contain small quantities of conjugated isomers and larger quantities of goemetrical isomers of linoleic acid. In either case the desired product is contaminated with closely related compounds. McKay and Bader [13] used *threo-* and *erythro*-9 : 10-dihydroxyoctadec-12-enoic acid, prepared from linoleic acid by partial bromination at the 12 : 13-positions, oxidation of the 9 : 10-double bond by permanganate or per-acid, and subsequent debromination. We consider these acids, isomeric with our dihydroxyoleic acids, should be solid, though McKay and Bader obtained only the *erythro*-isomer as a solid. Although their oily *threo*-compound was hydrogenated to *threo*-9 : 10-dihydroxystearic acid we consider it unlikely that it was pure.

Details of the oxidations are given in the Experimental section and the results are summarised in Tables 2 and 3. The high yield from the performic acid oxidation is in accordance with that usually obtained with monoethenoid compounds [23] and is greater

TABLE 3. 9 : 10 : 12 : 13-*Tetrahydroxystearic acids.*

	threo-9 : 10-*threo*-12 : 13- (VII, VIII)		*erythro*-9 : 10-*threo*-12 : 13- (III, IV)		*threo*-9 : 10-*erythro*-12 : 13- (V, VI)		*erythro*-9 : 10-*erythro*-12 : 13- (I, II)	
Yield of mixed tetrahydroxystearic acids (%)	82		61		92		59	
Yield of separated acids :								
(i) separated as acids (%) *	8	34	17	6	21	41	24	13
(ii) separated as esters (%) *	—	—	20	1·1	25	25	26	17
Acid, m. p.	147·5—148·5°	121—122°	164—165°	**112—113°**	**156·5—157°**	**129·5—131°**	176·5—177°	**155·5—156·5°**
C (%) †	62·1	62·0	62·0	62·2	62·1	61·9	62·2	62·1
H (%) †	10·5	10·3	10·6	10·1	10·6	10·6	10·4	10·5
Methyl ester, m. p.	—	—	135·5—136°	—	144·5—145·2°	113·5—115°	**170·5—171°**	143—146°
C (%) ‡	—	—	62·8	—	62·8	63·0	62·8	63·1
H (%) ‡	—	—	10·3	—	10·6	10·8	10·7	10·3
Racemic compound : [13, 14]								
acid, m. p.	148°	126°	**164°**	126°	164°	142°	174°	164°
ester, m. p.	118°	95°	—	—	—	—	157°	145·5°

* Based on the total theoretical yield. † $C_{18}H_{36}O_6$ requires C, 62·0, H, 10·4%.
‡ $C_{19}H_{38}O_6$ requires C, 63·0; H, 10·6%.
M. p.s in heavy type differ appreciably from those quoted for the racemic compound.

than in the oxidation of linoleic acid.[14, 24] The yields of separated tetrahydroxy-acids are much higher than those reported by McKay and Bader.[13]

We consider our products to be optically active for three reasons. The starting materials are active and it is believed that oxidation will not affect the asymmetric centres present; thus, the 9 : 10 : 12-trihydroxystearic acids obtained by oxidation of ricinoleic acid are optically active.[25] Several, though not all, of our tetrahydroxystearic acids show significant optical rotation (this refers to the observed rotation rather than to the calculated values of specific rotation). In some cases there is a marked difference in m. p. between the active and the inactive forms (see Table 3). The last may not be very strong

[23] Swern, "Organic Reactions," Vol. VII, p. 398, J. Wiley and Sons Inc., 1953.
[24] Swern and Dickel, *J. Amer. Chem. Soc.*, 1954, **76**, 1957.
[25] Kass and Radlove, *ibid.*, 1942, **64**, 2253.

evidence in all the instances cited since we consider some of the values quoted by McKay and Bader to be unsatisfactory, but one case is particularly strong, *viz.*, the high-melting form of methyl *erythro*-9 : 10-*erythro*-12 : 13-tetrahydroxystearate. We have confirmed McKay's value of 157° for the racemate whilst our active form has m. p. 171°.

In view of the frequency with which the m. p.s of active and inactive compounds of this type resemble one another it is interesting to relate our results to some conclusions by Kass and Burr [10] which have been questioned by McKay and Bader.[13] Kass and Burr obtained, from elaidinised linoleic acid, linelaidic acid and a liquid isomer considered to be the *trans*-9 : *cis*-12-acid from which they prepared two tetrahydroxystearic acids (m. p. 156—158°, 126—127°) by oxidation with dilute alkaline permanganate, presumably the *threo*-9 : 10-*erythro*-12 : 13-acids. McKay and Bader, however, report 164° and 142° for these acids (these were prepared from the *liquid* dihydroxyoctadecenoic acid and the higher-melting acid did not depress the m. p. of the higher-melting form of the *erythro*-9 : 10-*threo*-12 : 13-acid though the two are reported to have different crystalline properties) and consider that Kass and Burr's products are the *erythro*-9 : 10-*threo*-12 : 13-acids (m. p. 164°, 126°) which would be derived from the *cis*-9 : *trans*-12-octadecadienoic acid. On the other hand, our results (156°, 130°) suggest that Kass and Burr's original view may be correct, but since our products are enantiomorphic and theirs racemic this is not certain.

Experimental

threo-12 : 13-*Dihydroxyoleic Acid* (X).—This was isolated from *Vernonia anthelmintica* or *Cephalocroton cordofanus* seed oil by treatment with (i) acetic acid and (ii) alcoholic alkali as previously described.[14a] The dihydroxy-acid (m. p. 52—55°; 57% based on epoxy-acid present) was isolated by crystallisation from ether–light petroleum (b. p. 40—60°; 1 : 1) and then from ethyl acetate.

Partial Synthesis of Octadec-trans-12-*enoic Acid.*—*threo*-12 : 13-Dihydroxystearic acid [14a] (5 g.) was kept at room temperature for 16 hr. with a solution of hydrogen bromide in acetic acid (50 ml.; *d* 1·25) and concentrated sulphuric acid (5 ml.) and then heated to 100° for 8 hr., further hydrogen bromide reagent (5 ml.) being added after 4 hr. The solution was then cooled, diluted with water, and extracted with light petroleum (b. p. 60—80°). The crude *dibromide* (6·73 g., 97%) was purified by crystallisation from light petroleum (b. p. 40—60°) (5·13 g., 74%), m. p. 47·5—48·5° (Found : C, 49·0; H, 7·4; Br, 36·4. $C_{18}H_{32}O_2Br_2$ requires C, 48·9; H, 7·75; Br, 36·1%).

The dibromostearic acid (4·0 g.) was added to a mixture of zinc dust (8·7 g.), methanol (45 ml.), and aqueous hydrogen bromide (50%; 0·8 ml.) which had been refluxed for 5 min. and the whole boiled for 1 hr. in a nitrogen atmosphere. The filtered solution was extracted with ether; the extract, after being washed with alkali, contained only 0·07 g. of material, showing that practically no esterification had occurred. The alkaline solution when acidified and extracted gave the crude *trans*-acid (1·66 g., 65%) which after several crystallisations from methanol and acetone had m. p. 52—53° (lit.,[17] 52—53°) (Found : C, 76·6; H, 12·1. Calc. for $C_{18}H_{34}O_2$: C, 76·5; H, 12·1%).

This was converted into *threo*-12 : 13-dihydroxystearic acid, m. p. 96—97° (lit.,[17] 96·5—97°), by dilute alkaline permanganate and into the *erythro*-isomer, m. p. 117—118° (lit.,[17] 119—120°), by performic acid (Found : C, 68·1; H, 11·5. Calc. for $C_{18}H_{36}O_4$: C, 68·3; H, 11·5%).

erythro-12 : 13-*Dihydroxyoleic Acid* (XI).—*Cephalocroton cordofanus* seed oil (53 g.) was kept overnight in ether (1·5 l.) saturated with hydrogen bromide, and the solution was then washed with water and dried, and the solvent removed. The resulting bromohydrin (62 g.) was acetylated by boiling acetic anhydride (300 ml.) for 3 hr. and then heated with water (200 ml.) for a further 30 min., the product (64 g.) being isolated by ether-extraction. Silver acetate [prepared by slow addition of a solution of potassium acetate (20·8 g. in 75 ml. of water) to one of silver nitrate (32·8 g. in 75 ml. of water) and by subsequent washing of the precipitate with cold water and then with acetic acid] was added to the oily acetoxy-bromide (59 g.) dissolved in acetic acid (325 ml.) containing a little water (3·3 ml.) and refluxed for 8 hr. After filtering, the cold reaction mixture was diluted with water and extracted with ether, and the solvent removed from the extract after it had been washed and dried. The residue (54 g.) was finally hydrolysed with N-alcoholic potassium hydroxide (1·5 l.), and the mixed acids (45 g.)

were recovered by ether-extraction and then crystallised from ether. The erythro-12 : 13-*dihydroxyoleic acid* (21·3 g., 69% overall yield based on epoxy-acid originally present) was practically pure after the first crystallisation (m. p. 87—88°) (Found : C, 68·5; H, 10·8. $C_{18}H_{36}O_4$ requires C, 68·75; H, 10·9%).

The reaction proceeded equally smoothly with *V. anthelmintica* seed oil and we found (i) that the period of heating with silver acetate could be reduced to 2 hr. with an increase in yield (82%) and (ii) that a similar reaction occurred (45% in a single experiment) when the acetoxy-bromide was refluxed for 1 hr. with its own weight of silver nitrate in aqueous alcohol (10 ml. per g. of acetoxy-bromide).

The following derivatives were prepared by standard procedures : *methyl ester*, m. p. 56—57·5° (Found : C, 69·2; H, 11·2. $C_{19}H_{38}O_4$ requires C, 69·5; H, 11·1%); *ethyl ester*, m. p. 52—53° (Found : C, 70·1; H, 11·3. $C_{20}H_{38}O_4$ requires C, 70·1; H, 11·2%); p-*bromophenacyl ester*, m. p. 116—117° (Found : C, 61·1; H, 7·6; Br, 15·8. $C_{36}H_{59}O_5Br$ requires C, 61·1; H, 7·7; Br, 15·6%).

When hydrogenated over 5% palladium–charcoal the *erythro*-dihydroxyoleic acid (100 mg.) gave erythro-12 : 13-*dihydroxystearic acid* (90 mg.), m. p. 125—126° raised only to 125·5—126·5° after three crystallisations from ethanol and from ethyl acetate (Found : C, 68·3; H, 11·3. $C_{18}H_{36}O_4$ requires C, 68·3; H, 11·5%). The following esters were prepared : *methyl*, m. p. 102—103° (Found : C, 69·2; H, 11·6. $C_{19}H_{38}O_4$ requires C, 69·1; H, 11·6%); *ethyl*, m. p. 97—98° (Found : C, 69·7; H, 11·5. $C_{20}H_{40}O_4$ requires C, 69·7; H, 11·7%); p-*bromophenacyl*, m. p. 136·5—137·5° (Found : C, 60·6; H, 8·1; Br, 15·5. $C_{36}H_{61}O_5Br$ requires C, 60·8; H, 8·1; Br, 15·6%).

Oxidised [15a] with potassium permanganate in acetic acid solution at 45—50° *erythro*-12 : 13-dihydroxyoleic acid (1·80 g.) gave hexanoic acid (0·59 g.) (*p*-bromophenacyl ester, m. p. and mixed m. p. 70·5—71·5°; 63—64° when mixed with the ester of heptanoic acid), and azelaic acid (0·59 g.), m. p. and mixed m. p. 105—106°.

erythro-12 : 13-Dihydroxystearic acid (1·01 g.), similarly treated, afforded hexanoic acid (0·16 g.) (*p*-bromophenacyl ester, m. p. and mixed m. p. 71·5—72°; 62—63° when mixed with the ester of heptanoic acid), and dodecanedioic acid (0·23 g.), m. p. and mixed m. p. 129—131° (112—114° when mixed with sebacic acid).

erythro-9 : 10-threo-12 : 13-*Tetrahydroxystearic Acids* (III, IV).—*threo*-12 : 13-Dihydroxyoleic acid (5 g.), oxidised with dilute alkaline permanganate (potassium permanganate, 5·5 g.; sodium hydroxide, 5·0 g.) according to the procedure of Lapworth and Mottram,[26] gave crude tetrahydroxystearic acids (3·36 g.), insoluble in light petroleum (b. p. 40—60°).

A portion of these (1·60 g.) was separated by utilising the lower solubility of the higher-melting *acid* in ethyl acetate. This (437 mg.), after crystallisation from ethanol, melted at 164—165° (*methyl ester*, m. p. 135·5—136°). The lower-melting isomer, after repeated crystallisation from ethyl acetate and finally acetone, melted at 111—113°.

The remainder of the mixed acids (1·7 g.) was methylated (methanolic hydrogen chloride) and the methanol solution on progressive concentration gave several fractions of the higher-melting ester (576 mg.), m. p. 135—135·5°. The mother-liquors gave a small amount of solid, hydrolysed to the *acid* melting at 112—113°.

threo-9 : 10-threo-12 : 13-*Tetrahydroxystearic Acids* (VII, VIII).—*threo*-12 : 13-Dihydroxyoleic acid (6 g.) was boiled for 4 hr. with acetic anhydride (50 ml.) and for a further 2 hr. after the addition of water (50 ml.), and the product (7·23 g.) was isolated by ether-extraction. (The original dihydroxyoleic acid could be recovered in good yield after alkaline hydrolysis.) The diacetoxyoleic acid (5·4 g.), oxidised with formic acid (98%; 13 ml.) and hydrogen peroxide (25%; 2 ml.) by Swern's procedure,[23] gave a mixture of the di-*threo*-acids (4·54 g.) of which the greater part (3·87 g.) was insoluble in ether. This was extracted with acetone (6 × 50 ml.), and the last two extracts deposited, at room temperature, material (402 mg.) of m. p. 144—146° which was raised to 147·5—148·5° by several crystallisations from acetone and from ethyl acetate. The first two extracts gave crystals (2·12 g.) of m. p. 119—123° raised to 121—122° (1·59) by repeated crystallisation from acetone and from ethyl acetate.

When the dihydroxyoleic acid (5 g.) was similarly oxidised without prior acetylation the crude product (4·6 g.) gave a large ether-soluble fraction (2·53 g.; m. p. 63—68°) from which two products were isolated by fractional crystallisation : (*a*) m. p. 77·5—78·5° (Found : C, 65·2; H, 10·1. Calc. for $C_{18}H_{34}O_5$: C, 65·4; H, 10·4%); and (*b*) m. p. 94—95° (Found : C, 65·1; H, 10·0%). Our product (*b*) depressed the m. p. of compound A [14] (m. p. 95·5—96°) to 82—84° and of compound B [14] (m. p. 90—91°) to 81—83°.

[26] Lapworth and Mottram, *J.*, 1925, **127**, 1628.

erythro-9 : 10-erythro-12 : 13-*Tetrahydroxystearic Acids* (I, II).—*erythro*-12 : 13-Dihydroxyoleic acid (3 g.), dissolved in water (300 ml.) containing sodium hydroxide (3 g.), was diluted with 2·4 l. of water and then oxidised at 10° with potassium permanganate solution (1%; 290 ml.). After 5 min. the solution was decolorised with sulphur dioxide and, when acidified, gave crude tetrahydroxystearic acids (2·04 g.) of which the greater part (1·97 g.) was ether-insoluble. This was dissolved in ethanol and that part which crystallised at room temperature (1·39 g.), after several extractions with ethyl acetate and with acetone in which the *acid* is insoluble, was finally crystallised from aqueous ethanol, m. p. 176·5—177° (780 mg.); the *methyl ester* had m. p. and mixed m. p. with sample described below 170·5—171°. The low-melting *acid* was obtained from the ethanol mother-liquors and from the ethyl acetate and acetone extracts; a long series of crystallisations from ethyl acetate, aqueous alcohol, water, chloroform–acetic acid, acetone, and ethanol did not raise the m. p. above 155·5—156·5° (440 mg.). This was depressed to 145—150° on admixture with a sample of the *threo*-9 : 10-*erythro*-12 : 13-acid (m. p. 157°).

A sample of the mixed tetrahydroxy-acids (3·6 g.) was methylated by boiling it with methanolic hydrogen chloride. The product in methanol (150 ml.) deposited a large fraction at room temperature (2·14 g.; m. p. 159—165°) and a further fraction at 0° (0·96 g.; m. p. 143—144°). The m. p. rose sharply to 169—171° (1·50 g.) when the former was recrystallised from the same solvent and remained unchanged when the ester was washed with alkali; hydrolysis afforded the di-*erythro*-acid, m. p. 176·5—177·5°. The low-melting *ester* was unchanged in m. p. after several crystallisations or after washing with alkali; hydrolysis gave the low-melting di-*erythro*-acid.

The two racemic di-*erythro*-acids (m. p. 171·5—172·5°, 154—156°) were prepared by oxidation of linoleic acid; the methyl ester of the higher-melting acid had m. p. 157—157·5° confirming the value given by McKay *et al.*[14]

threo-9 : 10-erythro-12 : 13-*Tetrahydroxystearic Acid* (V, VI).—*erythro*-12 : 13-Dihydroxyoleic acid (5 g.) was acetylated and the product (6·23 g.) oxidised with performic acid, as already described. The greater part (5·02 g.) of the product (5·13 g.) was insoluble in ether.

A portion of the acids (2·5 g.), extracted with acetone and then with ethyl acetate, gave the high-melting *acid* as an insoluble fraction (574 mg.), m. p. 155—158° which became 156·5—157° after crystallisation from ethanol and repeated extraction with acetone and with ethyl acetate. The crystals which separated from the first acetone extracts were combined (1·27 g.; m. p. 128—131°). After repeated crystallisation from ethyl acetate and from ethanol this *acid* had m. p. 129·5—131°.

The remaining acids were esterified with cold methanolic hydrogen chloride, and the solution, when concentrated, gave crystals of *ester* (792 mg.), m. p. 142—145° raised to 144·5—145·5° after crystallisation from acetone, ethyl acetate, and methanol. Hydrolysis gave the higher-melting acid, m. p. and mixed m. p. 155·5—157°. Further concentration of the original methanol solution gave crude samples (1·63 g.) of the low-melting *ester*, purified by crystallisation from acetone, ethyl acetate, and methanol to m. p. 113·5—115° (720 mg.). Hydrolysis gave the low-melting acid, m. p. and mixed m. p. 130—131°.

The authors thank Dr. S. Krishna (Scientific Advisor to the High Commissioner of India in the U.K. and Scientific Liaison Officer) for supplying *V. anthelmintica* seeds, Mr. D. N. Grindley (Khartoum) for *C. cordofanus* seeds, Dr. A. F. McKay for certain samples used in mixed m. p. determinations (see p. 1618), and the J. N. Tata Endowment for the Higher Education of Indians (Bombay) for financial assistance (to K. E. B.).

Chemistry Department, University of St. Andrews. [*Received, November 22nd*, 1955.]

320. *Intermediates for the Synthesis of Optically Active Methyl-substituted Long-chain Acids. Part I.*

By R. Brettle and N. Polgar.

D-(+)-6-Methoxy-3-methylhexanoic acid * has been prepared from *L*-(+)-(methyl hydrogen β-methylglutarate) by anodic coupling with β-methoxypropionic acid. (+)-γ-Methoxy-α-methylbutyric acid was obtained by resolution of the racemic acid with cinchonidine methohydroxide.

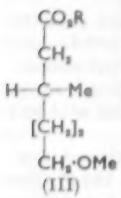
The present work was initiated in connection with studies in the syntheses of mycolipenic (I) and mycoceranic acid (II).[1] Concurrently with other approaches we turned our attention to methyl-substituted carboxylic acids with a terminal ether grouping as possible intermediates for these syntheses, with a view to utilising one of the functional groups for elaborating, in the correct configuration, the terminal structures of the naturally occurring acids, and the other functional group for attaching the requisite long carbon chain. Some preliminary work which included the preparations of *D*-(+)-6-methoxy-3-methylhexanoic and (+)-γ-methoxy-α-methylbutyric acid is now placed on record.

$CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH{:}CMe \cdot CO_2H$ (I)

$CH_3 \cdot [CH_2]_{21} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ (II)

Initial attempts to resolve α-methyl-γ-phenoxybutyric acid [2] met with no success. We next converted the foregoing acid by a Bouveault–Blanc reduction of its ethyl ester into 2-methyl-4-phenoxybutan-1-ol but, after an unsuccessful attempt to resolve the corresponding hydrogen phthalate, this approach was not pursued further.

We then turned to the use of *L*-(+)-(methyl hydrogen β-methylglutarate).[3,4] Anodic coupling of the latter with β-methoxypropionic acid, readily obtainable from acrylonitrile and methanol,[5] furnished methyl *D*(+)-6-methoxy-3-methylhexanoate (III; R = Me) (the change of the prefix *L* to *D* is due to alteration of the reference group *), which on hydrolysis gave the corresponding acid (III; R = H), $[\alpha]_D$ +6·1°. However, the low yield of the mixed electrolysis, together with the numerous stages required for obtaining the optically active starting material, did not encourage further work along these lines.


(III)

Therefore, we examined the resolution of γ-methoxy-α-methylbutyric acid, easily accessible by a malonic ester synthesis from 2-methoxyethyl bromide and ethyl methylmalonate (cf. ref. 6). In attempts to crystallise the cinchonidine or cinchonine salt of the butyric acid the free bases separated from the solutions; hence we turned to the quaternary ammonium hydroxides obtainable from the natural bases as resolving agents (cf. ref. 7). Resolution of the acid was readily accomplished with cinchonidine methohydroxide, affording the (+)-enantiomer, $[\alpha]_D$ +12·2°; cinchonidine methohydroxide for which there appears to be no previous record was prepared *via* the methiodide. Resolutions with quinine and its methohydroxide [7] are also reported in the Experimental section.

Experimental

Optical rotations were measured in a 0·5-dm. tube, unless otherwise stated.

α-Methyl-γ-phenoxybutyric Acid.—This was prepared, as described by Bentley, Haworth, and Perkin,[2] by a malonic ester synthesis from 2-phenoxyethyl bromide and ethyl methylmalonate. The brucine salt, prepared by dissolving equimolecular amounts of the acid and alkaloid in ethanol, did not crystallise. When the strychnine salt, obtained from chloroform

* The symbols *D* and *L* are used in the sense defined by Linstead *et al.* (*J.*, 1950, 3333).

[1] Polgar, *J.*, 1954, 1008, 1011; Marks and Polgar, *J.*, 1955, 3851.
[2] Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 171.
[3] Ställberg-Stenhagen, *Arkiv Kemi, Mineralog. Geol.*, 1947, **25**, *A*, No. 10.
[4] Linstead, Lunt, and Weedon, *J.*, 1950, 3333.
[5] MacGregor and Pugh, *J.*, 1945, 535.
[6] Prelog and Zalan, *Helv. Chim. Acta*, 1944, **27**, 531.
[7] Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.

solution, was dissolved in hot methanol and the solution cooled, crystals were deposited which were mainly strychnine. The cinchonidine salt also gave the free base on attempted crystallisation from aqueous methanol or acetone.

2-Methyl-4-phenoxybutan-1-ol.—Ethyl α-methyl-γ-phenoxybutyrate (22·2 g.; obtained from the foregoing acid by means of ethanolic sulphuric acid) was reduced with sodium (12 g.) and butanol (200 g.) (cf. ref. 8). *2-Methyl-4-phenoxybutan-1-ol*, b. p. 160°/18 mm., was obtained as a viscous oil (9·7 g.) (Found: C, 73·1; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 100—120°) as white plates, m. p. 81° (Found: C, 75·8; H, 6·3; N, 4·1. $C_{22}H_{23}O_3N$ requires C, 75·6; H, 6·6; N, 4·0%). The *hydrogen phthalate* had m. p. 55—57° (Found: C, 69·3; H, 6·3. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%); an attempt to resolve it with brucine failed.

β-Methoxypropionic Acid.—MacGregor and Pugh's procedure [8] was followed. Acrylonitrile (106 g., 1 mol.), methanol (64 g., 1 mol.), and 2% aqueous sodium hydroxide were shaken until no more heat was evolved (20 min.). The upper layer was then separated, neutralised with glacial acetic acid, dried (Na_2SO_4), and distilled. The resulting β-methoxypropionitrile (103 g., 60%), b. p. 164°, when heated under reflux with concentrated hydrochloric acid afforded β-methoxypropionic acid, b. p. 113—114°/17 mm. (Jones and Power [9] give b. p. 126°/30 mm.).

D-(+)-*6-Methoxy-3-methylhexanoic Acid* (III; R = H).—*L*-(+)-(Methyl hydrogen β-methylglutarate), $\alpha_D^{17.5}$ +0·32° (homogenous), was obtained by Ställberg-Stenhagen's procedure [3] with the modifications suggested by Linstead, Lunt, and Weedon.[4] The half-ester (8 g., 1 mol.) and β-methoxypropionic acid (10·4 g., 2 mol.) were added to a solution of methoxide [from sodium (0·5 g.) and methanol (250 c.c.)], and the mixture electrolysed in a cell containing two parallel platinum plate cathodes (2 × 3 cm.) set 1 cm. apart with a single platinum plate anode placed between (the apparatus was kindly lent by Dr. A. S. Bailey). The cell was cooled by immersion in an ice-bath and a current of about 2·3 amps. was passed until the solution became alkaline (1·5 hr.). It was then neutralised with glacial acetic acid and evaporated. Ether (50 c.c.) and 5% aqueous sodium carbonate (50 c.c.) were added to the residue, and, after the mixture had been shaken, the ethereal layer was separated, dried ($MgSO_4$), and distilled. Five runs on the above scale were worked up together, and the fraction, b. p. 99—101°/14 mm. (7·2 g., 16%), was hydrolysed by refluxing it with a solution of potassium hydroxide (4 g.) in water (20 c.c.) and ethanol (20 c.c.) for 3 hr. The solution was concentrated and extracted with ether to remove non-acidic material. Acidification of the aqueous phase, followed by extraction with ether and distillation, gave, after rejection of a small fore-run, D-(+)-*6-methoxy-3-methylhexanoic acid*, b. p. 149—151°/12 mm., n_D^{18} 1·4382, $[\alpha]_D^{18}$ +6·14° (*c*, 5·1 in ether; *l*, 1) (Found: C, 59·7; H, 10·2. $C_8H_{16}O_3$ requires C, 60·0; H, 10·0%). The *S-benzylthiuronium* salt had m. p. 136·5° (from ethanol) (Found: C, 58·9; H, 8·2; N, 8·4. $C_{16}H_{26}O_3N_2S$ requires C, 58·9; H, 8·0; N, 8·6%).

Resolution of γ-Methoxy-α-methylbutyric Acid.—An aqueous solution of cinchonidine methohydroxide was prepared by the following alternative procedures. (i) Methyl iodide (23·6 g., 1 mol.) was added to cinchonidine (49 g., 1 mol.) and ethanol (50 c.c.), and the mixture set aside overnight; crystallisation from hot water gave pale yellow needles of cinchonidine methiodide (55·8 g.). This was shaken with freshly precipitated silver oxide (from 70 g. of silver nitrate) and water (150 c.c.) at 0° for 15 min., then at room temperature for a further 3 hr. The aqueous solution was then decanted and filtered, and the filtrate centrifuged to remove colloidal silver oxide.

(ii) Cinchonidine methiodide (30 g.; prepared as above) was shaken with freshly precipitated silver chloride (from 10 g. of silver nitrate) and water (175 c.c.) for 2 hr.; the mixture was then heated and filtered while hot. Saturation of the cold filtrate with sodium chloride precipitated crude cinchonidine methochloride which was reprecipitated from filtered solution in dry ethanol by the addition of ether. After repetition of this purification process, the resulting methochloride was shaken with silver oxide (from 12 g. of silver nitrate) and water (20 c.c.) as above; the mixture was then filtered and the filtrate set aside overnight. A further filtration through Whatman No. 2 paper gave a clear solution of the methohydroxide.

The resulting solutions of cinchonidine methohydroxide were standardised by titration with 0·088N-sulphuric acid, phenolphthalein being used as indicator.

(±)-γ-Methoxy-α-methylbutyric acid (6·45 g., 1 mol.; obtained by Prelog and Zalan's method [6] from 2-methoxyethyl bromide [10] and ethyl methylmalonate) was added to aqueous

[8] Blatt, *Org. Synth.*, Coll. Vol. II, 1943, p. 468.
[9] Jones and Power, *J. Amer. Chem. Soc.*, 1924, **46**, 2530.
[10] Palomaa and Kenetti, *Ber.*, 1931, **64**, 797.

cinchonidine methohydroxide (0·32N; 153 c.c., 1 mol.), the solution filtered and then evaporated, and the residual salt dried *in vacuo* (P_2O_5). After four crystallisations from dioxan the cinchonidine methosalt (3·5 g.) was obtained as white needles, $[\alpha]_D^{16.5}$ −100° (*c*, 3·06 in EtOH); the rotatory power was unaltered on further recrystallisation. The salt was decomposed with 2N-hydrochloric acid and the liberated acid isolated by extraction with ether. On removal of the solvent the (+)-*acid* (0·8 g.) was obtained with $[\alpha]_D^{16.5}$ +12·2° (*c*, 15·28 in Et_2O).

Concentration of the mother-liquors from the above crystallisations, followed by the addition of dry ether, gave a further fraction of the cinchonidine methosalt which on decomposition as before afforded the partially resolved (−)-enantiomer (0·9 g.), $[\alpha]_D^{16.5}$ −6·9° (*c*, 17·30 in Et_2O).

In small-scale experiments the partially resolved (+)-enantiomer was obtained by resolution with quinine or quinine methohydroxide.[7] The quinine salt, prepared in acetone solution, crystallised from acetone–light petroleum (b. p. 40—60°), and the quinine methosalt (obtained as described above for the cinchonidine methosalt) from alcohol–ether.

The work was carried out during the tenure of a Nottinghamshire Senior Scholarship by one of us (R. B.).

Dyson Perrins Laboratory, Oxford University. [*Received, December 2nd*, 1955.]

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321. *The Selective Absorption of Optical Antipodes by Proteins. Part III.**

By William Bradley and Richard A. Brindley.

Wool which had previously combined with sulphuric acid or 1-*p*-sulphophenylazo-2-naphthol combines with, and resolves, a reduced amount of mandelic or *p*-heptyloxymandelic acid. The results indicate that the anions of sulphuric acid and the arylazo-sulphonic acid also become attached to ammonium centres in wool, and that the numbers of sites on which the resolution of mandelate anions can occur is limited. A similar conclusion was reached from a study of *m*-nitromandelic acid and 5-(2 : 4-dinitroanilino)-2-*p*-toluidinobenzenesulphonic acid.

In previous communications [1] it was shown that mandelic acid and many of its derivatives and analogues are resolved on wool by selective absorption of one of the optical antipodes from aqueous or aqueous-alcoholic solutions. The question arises whether the number of sites on which selective absorption of one of these antipodes can occur is constant. The present investigation indicates that the number is fixed, and this leads to the possibility of investigating the number of sites occupied by other, non-resolvable acids. The method of experiment adopted was to determine the amount and rotation of mandelic acid absorbed by wool under standard conditions, then to determine the extent to which the absorption and resolution were affected by the previous absorption of other non-resolvable acids. When the wool was allowed to react first with dilute aqueous sulphuric acid the amount of mandelic acid taken up was reduced, but the degree of resolution of the combined acid was not significantly altered. The result accords with the view that when sulphuric acid combines with wool the sulphate anions become attached to the same basic centres as mandelate ions would occupy in the absence of sulphuric acid. The hypothesis that sulphate ions become bound to specific sites in wool is supported by two previous investigations.[2] Removal of the sulphuric acid by repeated contact with water or aqueous ammonia restored the original capacity of the fibre to combine with and resolve mandelic acid. Evidently wool contains a limited number of basic sites which are capable of binding and resolving the anions of mandelic acid.

In a further experiment wool was first caused to take up 1-*p*-sulphophenylazo-2-naphthol

* Part II, *J.*, 1953, 1519.

[1] Bradley and Easty, *J.*, (*a*) 1951, 499; (*b*) 1953, 1519; Bradley, Brindley, and Easty, *Discuss. Faraday Soc.*, 1954, **16**, 152; Bradley and Brindley, *Nature*, 1954, **173**, 312; *Chem. and Ind.*, 1954, 579.

[2] Olofsson, *J. Soc. Dyers and Colourists*, 1952, **68**, 506; Underwood and White, *Discuss. Faraday Soc.*, 1954, **16**, 66.

from aqueous solution and then immersed in aqueous mandelic acid. The amount of mandelic acid combined and the degree of resolution were reduced by the absorbed azo-compound, the effect increasing with the amount of azo-compound present. The result favours the view that the anions of 1-*p*-sulphophenylazo-2-naphthol also are bound at the sites which would be occupied by mandelate ions in the absence of the azo-compound. As more sites are occupied by anions of the azo-compound more of the mandelic acid is bound non-selectively, possibly by hydrogen bonding at amide groups.[3] Wool which is saturated with 1-*p*-sulphophenylazo-2-naphthol (0·8 mole per kg. of wool) combines with, but does not resolve, mandelic acid.

Bradley, Brindley, and Easty [1] have shown that *p*-heptyloxymandelic acid also combines with and is resolved by wool. We now find that when wool is previously combined with 1-*p*-sulphophenylazo-2-naphthol the uptake and degree of resolution of *p*-heptyloxymandelic acid are both reduced; also that little or none of the combined azo-compound was replaced on the fibre by *p*-heptyloxymandelic acid, even after five weeks at the room temperature.

m-Nitromandelic acid also combines with and is resolved by wool. Wool which had previously combined with 5-(2 : 4-dinitroanilino)-2-*p*-toluidinobenzenesulphonic acid combined with a reduced amount of *m*-nitromandelic acid, and the rotation of the absorbed *m*-nitromandelic acid was too small to be recorded.

Experimental

p-*Ethoxymandelic Acid.*—Ethyl *p*-hydroxymandelate (19 g.) and ethyl iodide (32 g.) were refluxed in dry acetone (200 c.c.), freshly ignited potassium carbonate (40 g.) being added during 1 hr. After 3 hr. the suspension was cooled and filtered, the solid was washed with acetone, and the combined filtrates were evaporated. The residue (18 g.) was heated for 1 hr. under reflux with 4% aqueous sodium hydroxide (250 c.c.). The resulting solution was cooled, then acidified, and extracted with ether. The dried ($CaCl_2$) extracts gave almost pure p-*ethoxymandelic acid*. Crystallisation from benzene afforded 13 g. of acid, m. p. 129—130°, raised to 131° after further recrystallisation from benzene (Found : C, 61·6; H, 6·0. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1).

p-*Pentyloxymandelic acid*, m. p. 117—118° (from benzene) (Found: C, 65·5; H, 7·5. $C_{13}H_{18}O_4$ requires, C, 65·5; H, 7·6%), and p-*heptyloxymandelic acid*, m. p. 98° (from benzene) (Found : C, 67·6; H, 7·7. $C_{16}H_{24}O_4$ requires C, 67·7; H, 8·3%), were similarly prepared.

p-*Decyloxymandelic Acid.*—(*a*) Sodium *p*-decyloxymandelate (4 g.) resulted by the refluxing of ethyl *p*-hydroxymandelate (10 g.), decyl iodide (13·4 g.), and potassium carbonate (10 g.) in acetone (100 c.c.) and subsequent treatment with a solution of sodium in aqueous alcohol. The free *acid* (3·2 g.) had m. p. 105—106° (Found : C, 70·1; H, 9·1. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·1%), from benzene. (*b*) *p*-Hydroxybenzaldehyde (6·1 g.), decyl iodide (13·4 g.), and potassium carbonate (10 g.) were refluxed for 5 hr. The suspension was filtered, then evaporated, and the residue was dissolved in ether. The solution was cooled in ice–salt, liquid hydrogen cyanide (6 c.c.) was added, and after 12 hr. the product was isolated by evaporation under reduced pressure. Dry alcohol (4 c.c.) was added and the miminum volume of dry ether to give a solution, which was then saturated with dry hydrogen chloride at 0—5°. A deep red colour developed and crystals separated. These were collected, washed with ether, then dissolved in water (500 c.c.). Ethyl *p*-decyloxymandelate (7·5 g.) separated from the solution. The ethyl ester was refluxed for 2 hr. with a solution of sodium (2·6 g.) in alcohol (50 c.c.) containing water (2 c.c.). Crystals of sodium *p*-decyloxymandelate separated (6 g.). Acidification gave *p*-decyloxymandelic acid (5 g.), m. p. 105—106°, from benzene, identical with the product described in (*a*).

p-*Dodecyloxymandelic acid* separated from benzene as crystals, m. p. 108° (Found : C, 72·0; H, 9·4. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·5%).

p-*Hexadecyloxymandelic acid* had m. p. 111° (Found : C, 73·9; H, 10·0. $C_{24}H_{40}O_4$ requires C, 73·5; H, 10·2%).

2-*Oxalodibenzopyran* (Ring Index No. 1719).—Finely powdered aluminium chloride (32 g.) was stirred with dibenzopyran (33·4 g.) and ethoxalyl chloride (27·4 g.) in dry carbon disulphide (300 c.c.).[4] The mixture became red, then black and viscous. When hydrogen chloride was no

[3] Cf. T. Vickerstaff, "The Physical Chemistry of Dyeing," Oliver and Boyd, London, 1950, p. 301.
[4] Cf. Adickes, Brunnert, and Luckner, *J. prakt. Chem.*, 1931, **130**, 168.

longer liberated the mixture was refluxed for 2 hr. and then evaporated. The residue was added to ice and hydrochloric acid, and the yellow product was taken up in ether and recovered by evaporating the extract. It was then heated for 2 hr. with sodium hydroxide (20 g.) in water (200 c.c.) and alcohol (300 c.c.), most of the alcohol being evaporated in the process. On being cooled the residue gave golden-yellow crystals; these were collected and washed twice with ice-water, once with acetone, and thrice with ether (yield, 25 g.). Some of the purified sodium salt was dissolved in water, the solution was acidified, and the precipitated 2-*oxalodibenzofuran* was extracted with ether, recovered, and finally recrystallised thrice from benzene. It formed yellow granules, m. p. 146° (Found: C, 69·9; H, 3·2. $C_{14}H_8O_4$ requires C, 70·0; H, 3·3%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 228° (Found: N, 12·7. $C_{20}H_{12}O_7N_4$ requires N, 13·3%), formed brick-red crystals from alcohol.

Dibenzofuran-2-carboxylic Acid.—The above acid (1 g.) was dissolved in warm dilute sodium carbonate and 4% aqueous potassium permanganate was stirred in until excess was present. The solution was decolorized with sulphur dioxide, and the precipitated acid (0·7 g.) was collected, washed, and crystallised from chlorobenzene to give colourless prisms, m. p. 255° (softening at 235°) (Found: C, 73·5; H, 3·3. Calc. for $C_{13}H_8O_3$: C, 73·6; H, 3·8%). Mayer and Krieger [6] record m. p. 246—247° with softening at 237°.

2-*Dibenzofuranylglycollic Acid.*—A solution of the sodium salt (10 g.) of the above glyoxylic acid in water (750 c.c.) was heated with sodium amalgam until decolorized. Acidification of the decanted solution gave colourless crystals, and these were taken up in ether and recovered (8 g.) by evaporation. Crystallisation from benzene gave the glycollic acid as prisms, m. p. 153—156° (Found: C, 69·4; H, 4·0. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·1%), which showed no reaction with 2 : 4-dinitrophenylhydrazine.

2-*Naphthylglycollic Acid.*—Ethyl 2-naphthylglyoxylate [6] was refluxed for 2 hr. with 5% aqueous-alcoholic sodium hydroxide (200 c.c.). On being cooled the resulting solution afforded golden-brown crystals. These were redissolved and heated with sodium amalgam until the solution was decolorized. Acidification of the cooled filtrate then gave 2-naphthylglycollic acid (14 g.). It was extracted with ether, recovered by evaporating, and crystallised (m. p. 155—156°) from toluene (Madelung and Oberwegner [7] record m. p. 157° for the same acid prepared from 2-naphthylglyoxal). The keto-acid gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 237° (Found: N, 14·0. $C_{18}H_{12}O_6N_4$ requires N, 14·7%). The hydroxy-acid did not form a derivative with 2 : 4-dinitrophenylhydrazine.

9-*Oxaloanthracene.*—Powdered anhydrous aluminium chloride (50 g.) was stirred at 0° for 0·5 hr. with a solution of anthracene (27 g.) in dry nitrobenzene (1500 c.c.). A solution of ethoxalyl chloride (21 g.) in nitrobenzene (20 c.c.) was added and the stirring was continued for 4 hr. The product was kept for 12 hr., then mixed with hydrochloric acid and ice. The solvent was distilled in steam, and the residual black tar (A) was refluxed for 3 hr. with aqueous 10% sodium hydroxide (750 c.c.). The hot solution on filtration and cooling gave golden-yellow plates (33 g.) of sodium salt. Acidification of a solution of the salt (1 g.) gave a dark orange precipitate (0·85 g.) of the *acid*, m. p. 186° (decomp.), which crystallised from toluene in granules of the same m. p. (Found: C, 77·3; H, 4·1. $C_{16}H_{10}O_3$ requires C, 76·8; H, 4·0%). The 2 : 4-dinitrophenylhydrazone had m. p. 240° from alcohol.

Oxidation. An aqueous solution of the sodium salt was warmed with excess of potassium permanganate. The resulting suspension was decolorised by sulphur dioxide and the precipitate of slender, yellow needles was collected. The m. p. was 284°, alone or when mixed with anthraquinone.

Ethyl ester. In a repetition of the above preparation with 9 g. of anthracene the product (A) was extracted with ether, and the soluble portion was recovered by evaporating the solvent. It was a dark, orange product which crystallized. Recrystallisation from light petroleum (b. p. 60—80°) gave large, rectangular orange plates of 9-*ethoxalylanthracene*, m. p. 90° (5 g.). The same compound resulted when the glyoxylic acid (16 g.) was refluxed for 12 hr. with alcohol (100 c.c.) containing 2% of hydrogen chloride. On being cooled the solution afforded golden-yellow plates (12 g.), m. p. 85—90°, which gave pure ester, m. p. 90°, from light petroleum (Found: C, 77·7; H, 4·9. $C_{18}H_{14}O_3$ requires C, 77·8; H, 5·0%).

9-*Anthrylglycollic Acid.*—The preceding ester (12 g.; m. p. 85—90°) was heated on a steam-bath for 24 hr. with aluminium *iso*propoxide (10 g.) in dry *iso*propanol (100 c.c.). The solvent was then evaporated, the residue was mixed with dilute hydrochloric acid, and the product

[6] Mayer and Krieger, *Ber.*, 1922, **55**, 1661.
[6] Blicke and Feldkamp, *J. Amer. Chem. Soc.*, 1944, **66**, 1087.
[7] Madelung and Oberwegner, *Ber.*, 1932, **64**, 931.

was extracted with ether. Evaporation of the extract afforded a golden-yellow resin, and this was heated for 2 hr. with aqueous-alcoholic 5% sodium hydroxide (200 c.c.), the alcohol being allowed to evaporate. The residual solution was filtered, then cooled and acidified. The yellow, crystalline precipitate was extracted with ether, recovered (10 g., m. p. 95—100°), and recrystallised from toluene as *hemihydrate*, m. p. 104—106° (Found: C, 73·0; H, 5·3. $C_{16}H_{12}O_3,0{\cdot}5H_2O$ requires C, 73·6; H, 5·0%). Further crystallisation from ethyl acetate–light petroleum gave the *acid* as pale yellow plates, m. p. 116°, of *monohydrate* (Found: C, 70·7; H, 5·2. $C_{16}H_{12}O_3,H_2O$ requires C, 71·1; H, 5·2%) which showed no reaction with 2 : 4-dinitrophenylhydrazine.

9 : 10-*Dihydro*-9-*anthrylglycollic Acid.*—Sodium amalgam was stirred with a hot aqueous solution of sodium 9-anthrylglyoxylate (30 g.) until the liquid had become almost colourless. It was filtered, cooled, and acidified and the precipitated *acid* was extracted with ether. Evaporation gave 24 g. of pale orange crystals, m. p. 204—205°. Recrystallisation from toluene (charcoal) gave pale orange needles, m. p. 204—205° (Found: C, 75·4; H, 5·7. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

3-*Oxalopyrene.*—Powdered anhydrous aluminium choride (30 g.) was stirred with a solution of pyrene (18·5 g.) in dry carbon disulphide (150 c.c.). Ethoxalyl chloride (13 g.) was added and stirring was continued for 1 hr. The resulting suspension was heated for 3 hr. under reflux, then kept for 12 hr. at room temperature, and finally mixed with ice. The carbon disulphide was distilled off, and the oily suspension was heated with aqueous-alcoholic sodium hydroxide. Filtration and cooling gave yellow crystals of sodium 3-pyrenylglyoxylate (14 g.). The orientation of this acid is regarded as 3- in view of the work of Vollmann *et. al.*[8] Dissolution in water and acidification gave a precipitate of *acid* which separated from toluene as yellow granules, m. p. 138° (Found: C, 78·7; H, 3·9. $C_{18}H_{10}O_3$ requires C, 78·8; H, 3·7%). The 2 : 4-*dinitrophenylhydrazone* (Found: N, 12·6. $C_{24}H_{14}O_6N_4$ requires N, 12·3%) formed red-brown crystals, m. p. 231°, from alcohol.

By the Fischer–Speier method the acid gave its *ethyl ester* as prisms, m. p. 81° (from light petroleum (b. p. 100—120°) (Found: C, 78·5; H, 4·6. $C_{20}H_{14}O_3$ requires 79·5; H, 4·6%).

3-*Pyrenylglycollic Acid.*—This glyoxylate (8 g.) in dry *iso*propanol (100 c.c.) was refluxed for 24 hr. on a steam-bath with excess of aluminium *iso*propoxide. Evaporation gave a solid and this was extracted with ether after the addition of hydrochloric acid. Evaporation of the ether afforded a viscous, light-brown residue, and this was heated with aqueous-alcoholic sodium hydroxide, filtered, and acidified whilst hot. The 3-*pyrenylglycollic acid* which separated was extracted with ether, recovered by evaporation, and purified from *o*-dichlorobenzene. It formed light yellow crystals, m. p. 174° (decomp.) (Found: C, 78·0; H, 4·3. $C_{18}H_{12}O_3$ requires C, 78·3; H, 4·4%). A mixture of the acid with 3-pyrenylglyoxylic acid melted at 150—155°. It gave no reaction with 2 : 4-dinitrophenylhydrazine.

Absorption Experiments.—The wool employed in these experiments was Australian 64's Merino wool in the form of slubbing. It was cleaned as described by Bradley and Easty,[1a] and the method of experiment used by these authors was followed.

The weight of wool used was 25 g. in each experiment.

Table 1 shows the effect of previous treatment of wool with sulphuric acid on the subsequent absorption of mandelic acid. In the four experiments headed *B* wool was immersed in aqueous sulphuric acid, then in water, and finally in aqueous mandelic acid. Under *A* are two experiments in which the treatment with sulphuric acid was omitted. In each experiment a solution of 7·60 g. of mandelic acid in 500 c.c. of water was used and the duration of contact with wool was 40—45 hr., sufficient for equilibration. In experiments *B* (*a*), (*c*), and (*d*) the amount of sulphuric acid was 1·25 c.c. in 500 c.c. of water; in *B* (*b*) it was 25 c.c. in 500 c.c.

In *B* (*a*) the wool was heated for 2 hr. at 70° with the acid, then cooled, and finally rinsed in water (6 × 250 c.c.); in *B* (*c*) and (*d*) the final washing was with dilute ammonia until all [*B* (*d*)], or almost all [*B* (*c*)], sulphate ions were removed. In *B* (*b*) the same procedure was followed except that the heating was for 4·5 hr.

Table 2 shows the effect of (i) previously absorbed 5-(2 : 4-dinitroanilino)-2-*p*-toluidinobenzenesulphonic acid on the absorption of *m*-nitromandelic acid by wool, and (ii) the effect of previously absorbed 1-*p*-sulphophenylazo-2-naphthol on the absorption of *p*-heptyloxymandelic acid. In experiment 2 (*a*) the amount of the sulphonic acid previously absorbed by the wool was 7·5 g.; in 2 (*b*) it was 5·0 g. The treated wool was added in each experiment to a solution of the stated amount of *m*-nitromandelic acid in 500 c.c. of water; no measurable amount of

[8] Vollmann, Becker, Correll, and Streeck, *Annalen*, 1937, **531**, 1.

the sulphonic acid was displaced. The *m*-nitromandelic acid absorbed was recovered by means of dilute aqueous ammonia in 2 (*a*) and by immersion in water (6 × 500 c.c.) in 2 (*b*). Experiments 1 (*a*) and (*b*) show the amounts of *m*-nitromandelic acid which are absorbed from identical

TABLE 1.*

		A		*B*			
		(*a*)	(*b*)	(*a*)	(*b*)	(*c*)	(*d*)
Mandelic acid : absorbed	(g.)	2·93	2·80	1·66	1·24	2·44	2·74
	(mole) ...	0·019	0·018	0·011	0·008	0·016	0·018
Mandelic acid : unabsorbed	(g.)	4·55	4·60	5·72	5·85	5·06	4·73
	(mole) ...	0·03	0·03	0·038	0·038	0·033	0·031
Mandelic acid : recovered	(g.)	7·48	7·40	7·38	7·09	7·50	7·47
	(mole) ...	0·049	0·048	0·049	0·046	0·049	0·049
Rotation of absorbed acid		+0·29°	+0·29°	+0·17°	+0·10°	+0·25°	+0·28°
Rotation of unabsorbed acid		−0·26°	−0·29°	−0·20°	−0·21°	−0·24°	−0·28°
pH of filtrate		2·12	2·43	2·04	2·06	2·18	2·28

* For explanation of headings see text.

TABLE 2.

	m-Nitromandelic		(I) 5-(2 : 4-Dinitroanilino)-2-*p*-toluidinobenzenesulphonic (II) *m*-Nitromandelic		*p*-Heptyloxymandelic		(I) 1-*p*-Sulphophenylazo-2-naphthol (II) *p*-Heptyloxymandelic	
	1 (*a*)	1 (*b*)	2 (*a*)	2 (*b*)	3 (*a*)	3 (*b*)	4 (*a*)	4 (*b*)
m-Nitro- or *p*-heptyloxymandelic acid (g.) ...	9·00	9·85	9·00	9·85	6·65	6·65	4·19	4·91
m-Nitro- or *p*-heptyloxymandelic acid (mole)	0·046	0·05	0·046	0·05	0·025	0·025	0·016	0·018
Above acid : absorbed (g.)	4·82	5·44	1·54	1·58	3·93	3·60	1·99	1·17
Above acid : absorbed (mole) ...	0·025	0·028	0·008	0·008	0·015	0·014	0·007	0·004
Above acid : unabsorbed (g.)	3·89	4·17	7·56	6·86	2·88	2·78	2·22	3·70
Above acid : unabsorbed (mole) ...	0·020	0·022	0·038	0·35	0·011	0·010	0·008	0·014
Above acid : recovered (g.)	8·71	9·61	9·10	8·44	6·81	6·38	4·21	4·87
Above acid : recovered (mole) ...	0·045	0·049	0·046	0·043	0·025	0·024	0·016	0·018
Rotation of absorbed acid	+0·07°	+0·09°	—	—	+0·20°	+0·15°	+0·13°	+0·03°
Rotation of unabsorbed acid	−0·10°	−0·10°	—	—	−0·11°	−0·22°	−0·12°	+0·03°
pH of filtrate	2·28	2·14	2·06	1·94	—	—	—	—

TABLE 3.

1-*p*-Sulphophenylazo-2-naphthol on wool (mole)	0·003	0·008	0·009	0·012	0·012	0·014	0·016	0·020	0·021
Mandelic acid (absorbed (mole)	0·017	0·014	0·013	0·011	0·013	0·012	0·011	0·009	0·010
Rotation	+0·27°	+0·18°	+0·20°	+0·10°	+0·16°	(+0·10°)	(+0·06°)	+0·04°	(0°)
Mandelic acid unabsorbed (mole)	—	0·033	0·035	0·038	0·035	0·037	0·038	0·040	0·039
Rotation	−0·28°	−0·24°	−0·21°	−0·14°	−0·16°	−0·12°	−0·10°	(−0·04°)	(0°)
pH of mandelic acid solution	2·32	2·34	2·29	2·25	2·31	2·36	2·36	2·22	2·22
Mandelic acid recovered (mole)	—	0·047	0·048	0·049	0·048	0·049	0·049	0·049	0·049
Acids combined with wool (mole)	0·020	0·022	0·022	0·023	0·025	0·026	0·027	0·029	0·031

solutions to those used in 2 (*a*) and (*b*) when wool not previously treated with the sulphonic acid is used.

In experiment 4 (*a*) the amount of the sulphonic acid absorbed on the wool was 7·7 g., in 4 (*b*) it was 4·1 g. The *p*-heptyloxymandelic acid was used as a solution in 500 c.c. of aqueous alcohol containing 250 c.c. of alcohol. In 3 (*a*) and (*b*) the medium was 1 l. of aqueous alcohol containing 500 c.c. of alcohol.

Table 3 shows the amount of mandelic acid absorbed at equilibrium at the room temperature

by wool which had previously combined with the stated amounts of 1-*p*-sulphophenylazo-2-naphthol. The initial amounts of mandelic acid were 7·60 g. in 500 c.c. of aqueous solution. There was no measurable displacement of the sulphonic acid by mandelic acid.

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322. *Reactions of Organic Azides. Part VI.* The Interaction of 2-Acylbenzoic Acids and Alkylidenephthalides with Hydrazoic and Sulphuric Acids.*

By C. L. Arcus and R. E. Marks.

2-Acylbenzoic acids and alkylidenephthalides react with hydrazoic and sulphuric acids to yield, principally, 2-substituted 6-oxo-4 : 5-benz-1 : 3-oxazines; where the substituent is aryl, the oxazine is the isolated product under the conditions employed; where it is alkyl or aralkyl, the hydrolysis product, an *N*-acylanthranilic acid, is obtained. The mechanisms of this reaction, and of a subsidiary rearrangement, are discussed.

It has been shown (Part II,[1] and earlier observations by Badger, Howard, and Simons [2]) that the Schmidt reaction with 2-benzoylbenzoic acid proceeds as follows: reaction of the keto-acid (I; R = Ph) with sulphuric acid gives a cyclic cation (II) which combines with hydrazoic acid, yielding the protonated azide (III); the latter rearranges and undergoes ring-expansion to form the proton-adduct (VI) of 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine; addition of water (in the presence of chloroform as a protective solvent against hydrolysis) yields the benzoxazine (IV).

Seven 2-acylbenzoic acids (I; R representing groups of different electronic character, and size) have been subjected to the Schmidt reaction under standardised conditions in order to ascertain whether there is a relation between the nature of R and (*a*) the rate of oxazine formation and (*b*) the extent of rearrangement in the direction which leads, not to the oxazine, but (ultimately) to the amine R·NH_2. The results obtained are shown in the Table.

The reaction of 2-acylbenzoic acids and alkylidenephthalides with hydrazoic and sulphuric acids.

Benzoic acid	Principal product	Yield (%)	Amine	Yield (%)
	6-Oxo-4 : 5-benz-1 : 3-oxazine :			
2-*p*-Methoxybenzoyl-	2-*p*-Methoxyphenyl-	75	—	—
2-*p*-Chlorobenzoyl-	2-*p*-Chlorophenyl-	84	*p*-Chloroaniline	3
2-*m*-Nitrobenzoyl-	2-*m*-Nitrophenyl-	87	*m*-Nitroaniline	4
2-Mesitoyl-	2-Mesityl-	29	*	—
2-α-Naphthoyl-	2-α-Naphthyl-	51	α-Naphthylamine	7
	Anthranilic acid :			
2-Phenylacetyl-	*N*-Phenylacetyl-	85	—	—
2-Butyryl-	*N*-Butyryl-	77	Propylamine	5
Benzylidenephthalide	*N*-Phenylacetyl-	62	—	—
Propylidenephthalide	*N*-Butyryl-	69	Propylamine	5

* *N*-Mesitylphthalamidic acid (14%) isolated.

6-Oxo-2-phenyl- and -2-*p*-tolyl-4 : 5-benz-1 : 3-ozaxine have been obtained [1] in 80 and 88% yield, respectively, by a procedure almost identical with that of the present work. It is apparent from these results, together with those of the Table, that (apart from the reaction of 2-mesitoylbenzoic acid) the presence of groups of markedly different electronic

* Part V, *J.*, 1956, 1498.

[1] Arcus and Coombs, *J.*, 1953, 3698.

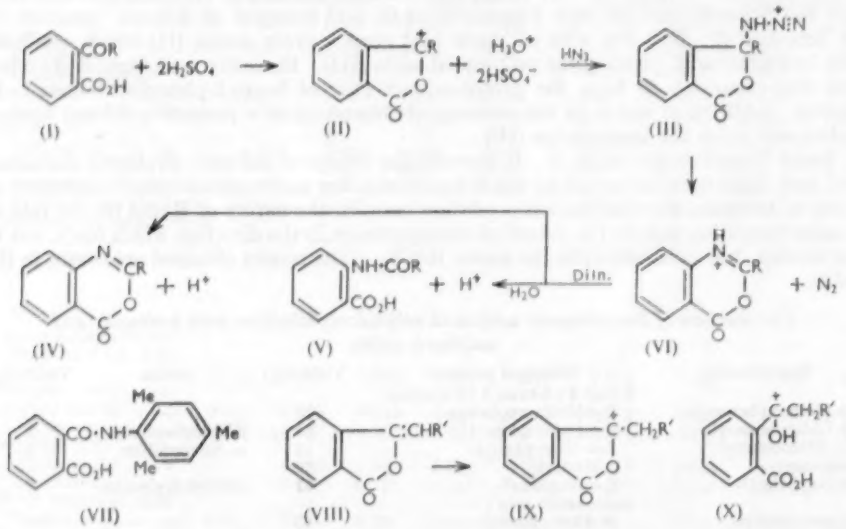
[2] Badger, Howard, and Simons, *J.*, 1952, 2849.

character (*p*-Me, *p*-MeO, *p*-Cl, *m*-NO_2) in the benzoyl group has little effect on the course of the reaction, the oxazine being isolated in 75—88% yield. The yield of oxazine from 2-α-naphthoylbenzoic acid was somewhat lower; that from 2-mesitoylbenzoic acid was comparatively small, and, unlike any other, this reaction yielded an appreciable amount of the phthalamidic acid (VII). 2-Phenylacetyl- and 2-butyryl-benzoic acid gave the *N*-acylanthranilic acids in yields which lie in the range of those of the phenyl-oxazines, above.

p-Chloro- and *m*-nitro-aniline, α-naphthylamine, and propylamine were characterised; the largest yield was that of α-naphthylamine, 7%.

By the use of procedures different from that of the present work, Badger *et al.*[2] have isolated the oxazine and *N*-α-naphthoylanthranilic acid, depending on the conditions, from the Schmidt reaction with 2-α-naphthoylbenzoic acid, and Smith [3] has obtained *N*-acetylanthranilic acid from the reaction with 2-acetylbenzoic acid.

Mechanism.—The cyclic cation (IX), which is formed from 2-phenylacetyl- and 2-butyryl-benzoic acid by the process (I) ⟶ (II), may also be formed by the protonation of the olefins benzylidene- and propylidene-phthalide (VIII); these compounds reacted similarly to the 2-acylbenzoic acids, giving the *N*-acylanthranilic acids in somewhat lower yields. That reaction succeeds with these olefins is considered to support the mechanism of reaction *via* the cyclic cation (IX), since the ion (X), derived from the protonation of the 2-acylbenzoic acid regarded simply as a ketone, could only arise by the hydration, as well as protonation, of the alkylidenephthalides, a process unlikely to occur in concentrated sulphuric acid.



Formation of N-acylanthranilic acids. The isolation of the N-acylanthranilic acid as end-product from the reaction when R is alkyl or aralkyl (see Table) is attributed to hydrolysis of the initially formed oxazine at the point where the chloroform–sulphuric acid reaction mixture is diluted with water. 2-Benzyl-6-oxo- and 6-oxo-2-propyl-4 : 5-benz-1 : 3-oxazine were prepared by ring closure of the corresponding *N*-acylanthranilic acids; each was then subjected to the conditions of the Schmidt reaction, but without sodium azide: hydrolysis occurred, and 97 and 88% yields, respectively, of the *N*-acylanthranilic acid were isolated.

The marked difference in ease of hydrolysis of 2-alkyl- and 2-aryl-oxobenzoxazines has

[2] Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 431.

been noted by Zentmeyer and Wagner [4] and is demonstrated by the following observations. 2-Benzyl, 2-propyl, and 2-*p*-chlorophenyl derivatives of 6-oxo-4 : 5-benz-1 : 3-oxazines were heated for 30 min. with 80% acetic acid and with 80% ethanol: from the 2-benzyloxazine 94 and 88% of phenylacetylanthranilic acid was isolated, and from the 2-propyloxazine 90 and 95% of butyrylanthranilic acid; of the *p*-chlorophenyloxazine 73 and 96% were recovered, 13% of chlorobenzoylanthranilic acid being isolated from the treatment with aqueous acetic acid.

Intermediates, and the "non-oxazine" rearrangement. It had been supposed that there might be a partition of the various products, or their precursors, in the above reactions, between the chloroform and the sulphuric acid layer. Accordingly, the following procedure was applied to the reactions with 2-*p*-chlorobenzoyl-, 2-mesitoyl-, and 2-butyrylbenzoic acid, compounds which yield as main end-products respectively oxazine, oxazine and phthalamidic acid, and *N*-acylanthranilic acid: the chloroform layer was separated at the end of the reaction, but before the addition of ice, and evaporated; in each instance it contained no solute. All the products at this stage of the above reactions are therefore present in the sulphuric acid layer, presumably as their hydrogen sulphates.

In completion of the above reactions, the separated sulphuric acid layers were added to ice; essentially the same products as those of the Table were obtained, except that the absence of chloroform as a diluent led to certain secondary reactions. The reaction with 2-*p*-chlorobenzoylbenzoic acid gave *N*-*p*-chlorobenzoylanthranilic acid together with a much reduced yield of the oxazine, a result ascribed to the hydrolysis of the oxazine, the occurrence of which, on dilution of a sulphuric acid solution of this compound, was directly confirmed. The analogous products have been obtained [1] from the Schmidt reaction with 2-benzoylbenzoic acid on dilution in the presence or absence of chloroform. The yield of 2-mesityl-6-oxo-4 : 5-benz-1 : 3-oxazine (26%) is close to that (see Table) obtained in the presence of chloroform, and no hydrolysis product was encountered; the greater resistance of this oxazine is attributed to protection of the site of hydrolysis by the *o*-methyl groups of the mesityl substituent. In one instance *N*-mesitylphthalamidic acid (22%) was obtained, but in two cases it had become cyclised to *N*-mesitylphthalimide (20%), the occurrence or absence of conversion of the phthalamidic acid into the phthalimide depending, apparently, on small variations in experimental conditions. From 2-butyrylbenzoic acid there was obtained *N*-butyrylanthranilic acid in nearly the same yield as recorded in the Table.

The mechanisms of formation of the amines and the phthalamidic acid of the Table are not completely understood; the following two points are relevant.

The extent of rearrangement with migration of the group R is seen to be greatest in the two examples (mesityl and α-naphthyl) in which R has the greatest bulk in the neighbourhood of the keto-carbon atom.

It appeared possible that the amine $R{\cdot}NH_2$ is formed by hydrolysis of the corresponding phthalamidic acid. Accordingly, *N*-*m*-nitrophenylphthalamidic acid was subjected to the conditions of the Schmidt reaction: *m*-nitroaniline (29%) was isolated, the remaining phthalamidic acid being partly recovered (39%), and in part isolated as the phthalimide. Hydrolysis of the phthalamidic acid is, therefore, too slow to account satisfactorily for the presence of the amine.

From the present and earlier results [1] it is concluded, with regard to the reaction of 2-acylbenzoic acids and alkylidenephthalides with hydrazoic and sulphuric acids, that: (*a*) The greater part of the reaction takes the following course: the protonated azide (III), formed by addition of hydrazoic acid to the cyclic cation (II), rearranges as shown to (VI); the benzoxazine is the isolated product of reaction if (i) R is aryl and (ii) chloroform is present as a protective solvent during dilution with water; in other circumstances the hydrolysis product of the oxazine, the *N*-acylanthranilic acid, is obtained. (*b*) Where $R = C_6H_4X$, the electronic character of the substituent X has little effect on the course of the reaction. (*c*) Migration of R is appreciable only when this group has exceptional bulk in the neighbourhood of the carbonyl-carbon atom.

[4] Zentmeyer and Wagner, *J. Org. Chem.*, 1949, **14**, 967.

Experimental

M. p.s are corrected.

Phthalic anhydride (30 g.), anisole (22 ml.), and aluminium chloride (60 g.) yielded, by Lin Che Kin's procedure,[5] 2-*p*-methoxybenzoylbenzoic acid (37 g.), m. p. 136—138°; after recrystallisation from ethanol and from toluene it (26 g.) had m. p. 145·5—146°. Lin Che Kin records m. p. 145°.

Phthalic anhydride (30 g.), chlorobenzene (122 ml.), and aluminium chloride (64 g.), on reaction according to Groggins and Newton,[6] gave 2-*p*-chlorobenzoylbenzoic acid (45 g.), m. p. 147°; on recrystallisation from benzene it (38 g.) had m. p. 150·5—151°. These authors record m. p. 147·5°.

2-Benzoylbenzoic acid (11·3 g.), on nitration according to Basler,[7] gave a product (13·8 g.) having m. p. 136—150°. This material was recrystallised from acetic acid, then dissolved in alkali, and the solution treated with charcoal and acidified; the product, thrice recrystallised from ethanol, yielded 2-*m*-nitrobenzoylbenzoic acid (2·90 g.), m. p. 189—189·5° (Basler records m. p. 186—187°).

Phthalic anhydride (15 g.), mesitylene (15 ml.), and aluminium chloride (30 g.), on reaction in *sym*-tetrachloroethane (75 ml.) by the method indicated by Newman and McCleary,[8] yielded 2-mesitoylbenzoic acid (24 g.), m. p. 215°; on recrystallisation from aqueous ethanol it (20 g.) had m. p. 214—214·5°. These authors record m. p. 214—216°.

Phthalic anhydride (100 g.), naphthalene (130 g.), and aluminium chloride (208 g.) gave, by Heller and Schulke's method,[9] a product (165 g.), m. p. 137—150°, which was rubbed with and filtered from cold acetic acid, then recrystallised from toluene and twice from ethanol; it yielded 2-α-naphthoylbenzoic acid (50 g.), m. p. 175·5—176°. Heller and Schulke record m. p. 173°.

Benzylidenephthalide[10] (31·3 g.; m. p. 100—100·5°) was heated with a solution of potassium hydroxide (30 g.) in water (100 ml.). The cooled solution was poured into a solution of sulphuric acid (40 ml.) in water (250 ml.); the product was collected and dissolved in aqueous sodium hydrogen carbonate. This solution was acidified with dilute hydrochloric acid until a faint permanent precipitate appeared; the whole was then extracted with chloroform (4 × 30 ml.). Excess of acid was added to the solution, and the product was collected, ground, washed and dried; it (32·0 g.), m. p. 72·5—73·5°, was twice recrystallised from ethanol–water (60 : 40) and yielded 2-phenylacetylbenzoic acid monohydrate (24·2 g.), m. p. 74·5—75° (Found: equiv., 259. Calc. for $C_{14}H_{11}O{\cdot}CO_2H,H_2O$: equiv., 258). Gabriel and Michael[11] record m. p. 74—75° for the monohydrate.

From phthalic anhydride (58·5 g.), butyric anhydride (125 g.), and sodium acetate (32·5 g.) there was prepared, by the procedure of Ullyot, Taylor, and Dawson,[12] propylidenephthalide (41 g.), b. p. 146—149°/4 mm. It contained needles of phthalic anhydride, which was removed as follows: the material was dissolved in ethanol (40 ml.) and 0·12N-sodium hydroxide was added until, when spotted on to phenolphthalein paper, the mixture proved alkaline. By this procedure phthalic anhydride would be expected to be quantitatively converted into sodium ethyl phthalate.[13] The solution was extracted with chloroform (2 × 50 ml.), and the extract was washed, dried (Na_2SO_4), and evaporated; the product gave, on distillation, propylidenephthalide (28 g.), b. p. 149—150°/4 mm., n_D^{20} 1·5824.

Propylidenephthalide (22·9 g.) was converted by the method of Ullyot *et al.*[12] into 2-butyrylbenzoic acid (23·2 g.), m. p. 84—85°; after purification *via* solution in aqueous sodium hydrogen carbonate, and two recrystallisations from ether–light petroleum (b. p. 40—60°), it (11·7 g.) had m. p. 90·5—91° (these authors record m. p. 86—89°).

Schmidt Reactions.—The above 2-acylbenzoic acids and alkylidenephthalides were subjected to the Schmidt reaction by the following standardised procedure. The names of products are given in square brackets at the points where, when present in sufficient amount, they were isolated.

[5] Lin Che Kin, *Ann. Chim. (France)*, 1940, **11**, 317.
[6] Groggins and Newton, *Ind. Eng. Chem.*, 1929, **21**, 369.
[7] Basler, D.R.-P. 148,110.
[8] Newman and McCleary, *J. Amer. Chem. Soc.*, 1941, **63**, 1540.
[9] Heller and Schulke, *Ber.*, 1908, **41**, 3633.
[10] *Org. Synth.*, Coll. Vol. II, 1st. Edn., p. 61.
[11] Gabriel and Michael, *Ber.*, 1878, **11**, 1018.
[12] Ullyot, Taylor, and Dawson, *J. Amer. Chem. Soc.*, 1948, **70**, 542.
[13] Anderson and Kenyon, *ibid.*, p. 3952.

Sulphuric acid (98%; 15 ml.) was added dropwise to a stirred, ice-cooled mixture of sodium azide (2·6 g., 0·040 mole) and chloroform (15 ml.). After a further 15 min., the ice was replaced by a water-bath maintained at 30°, and the 2-acylbenzoic acid or the alkylidenephthalide (0·0200 mole), in suspension or solution in chloroform (20 ml.), was added during 1 hr.; stirring was continued for 2 hr., the mixture was then poured on ice (200 g.). The whole, together with washes of water and chloroform (25 ml.), was shaken mechanically for ½ hr., and filtered [*N*-mesitylphthalamidic acid, and the bulk of the *N*-phenylacetylanthranilic acid]. The aqueous layer was extracted with chloroform (2 × 25 ml.), and the combined chloroform solutions were twice extracted with saturated aqueous sodium hydrogen carbonate, washed with water, dried (Na_2SO_4), and the solvent distilled [benzoxazines].

The sodium hydrogen carbonate extract was acidified with dilute hydrochloric acid, and the product filtered off [*N*-phenylacetyl- and *N*-butyryl-anthranilic acid].

The acidic aqueous solution was concentrated by distillation, filtered, brought to pH 10 with sodium hydroxide solution, and extracted with ether (2 × 50, 2 × 25 ml.). The extract was dried (Na_2SO_4), and the ether distilled [amines].

2-*p*-Methoxybenzoylbenzoic acid [(i), (ii) 5·12 g.)] yielded 2-p-*methoxyphenyl*-6-*oxo*-4 : 5-*benz*-1 : 3-*oxazine* [(i) 3·68, (ii) 3·87 g., from ethanol], needles, m. p. 157·5—158°, which had m. p. 158·5° after further recrystallisation (Found: C, 71·0; H, 4·45; N, 5·7. $C_{15}H_{11}O_3N$ requires C, 71·4; H, 4·4; N, 5·55%).

2-*p*-Chlorobenzoylbenzoic acid [(i), (ii) 5·21 g.] gave 2-*p*-chlorophenyl-6-oxo-4 : 5-benz-1 : 3-oxazine [(i) 4·31, (ii) 4·35 g., from *n*-butanol], m. p. 191° (Found: N, 5·55; Cl, 14·1. Calc. for $C_{14}H_8O_2NCl$: N, 5·45; Cl, 13·75%). Zentmeyer and Wagner [4] record m. p. 190°. There was also isolated an aromatic amine [(i) 0·07, (ii) 0·06 g.] having m. p. 62·5—63·5°, and m. p. 63—66° when mixed with *p*-chloroaniline of m. p. 70—71°; its benzoyl derivative, recrystallised from aqueous ethanol, had m. p. 192—193° alone and when mixed with *N*-benzoyl-*p*-chloroaniline of m. p. 194—194·5°.

2-*m*-Nitrobenzoylbenzoic acid [(i), (ii) 5·42 g.] yielded 2-*m*-nitrophenyl-6-oxo-4 : 5-benz-1 : 3-oxazine [(i) 4·61, (ii) 4·73 g., from *n*-butanol], m. p. 169·5—170° (Bogert, Gortner, and Amend [14] record m. p. 167—168°) (Found: N, 10·5. Calc. for $C_{14}H_8O_4N_2$: N, 10·45%). There was also isolated *m*-nitroaniline [(i) 0·11, (ii) 0·09 g.], having m. p. 113—114° alone and when mixed with an authentic specimen; its benzoyl derivative had m. p. 158° alone and when mixed with authentic *N*-benzoyl-*m*-nitroaniline.

2-Mesitoylbenzoic acid [(i), (ii) 5·36 g.] gave 2-*mesityl*-6-*oxo*-4 : 5-*benz*-1 : 3-*oxazine* [(i) 1·66, (ii) 1·39 g., from ethanol], m. p. 138—139°, which after two recrystallisations formed pale yellow plates, m. p. 142° (Found: C, 76·65; H, 5·7; N, 5·55. $C_{17}H_{15}O_2N$ requires C, 76·95; H, 5·7; N, 5·3%). There was also obtained *N*-*mesitylphthalamidic acid* [(i) 0·64 g., from ethanol; (ii) 1·01 g. from dioxan], m. p. 191·5—193° (decomp.) (the m. p. varied with the rate of heating) (Found: C, 72·5; H, 6·25; N, 5·3%; equiv., 282. $C_{16}H_{16}ON{\cdot}CO_2H$ requires C, 72·05; H, 6·05; N, 4·95%; equiv., 283). It (0·1 g.) was heated under reflux for ½ hr. with glacial acetic acid (1·3 ml.); to the cold solution water was added, the whole was warmed, and on cooling there separated needles of *N*-mesitylphthalimide having m. p. 180·5°, unaltered by recrystallisation from aqueous acetic acid and by admixture with an authentic specimen of the same m. p.

2-α-Naphthoylbenzoic acid [(i), (ii), (iii) 5·52 g.] yielded 2-α-naphthyl-6-oxo-4 : 5-benz-1 : 3-oxazine [(i) 2·51, (ii) 3·08, (iii) 2·78 g.], m. p. 137—138°; after recrystallisation, with charcoal treatment, from ethanol, it formed golden needles, m. p. 138° (Found: N, 5·1. Calc. for $C_{18}H_{11}O_2N$: N, 5·15%). Badger *et al.*[2] record m. p. 134°. There was also isolated a base [(i) 0·20, (ii) 0·15, (iii) 0·23 g.] which yielded a benzoyl derivative having m. p. 159·5° alone, and m. p. 161·5—162° when mixed with benzo-α-naphthalide of m. p. 162—162·5°.

Benzylidenephthalide [(i), (ii) 4·44 g.] and 2-phenylacetylbenzoic acid [(iii), (iv) 5·16 g.] both gave *N*-phenylacetylanthranilic acid [(i) 2·64, (ii) 2·11, (iii) 4·07, (iv) 3·86 g., from ethanol–water (1 : 1)], m. p. 186—189·5°; after further recrystallisation it had m. p. 189·5—190° (Diesbach *et al.*[15] record m. p. 188°) (Found: C, 70·35; H, 5·05; N, 5·6%; equiv., 255. Calc. for $C_{14}H_{13}ON{\cdot}CO_2H$: C, 70·5; H, 5·15; N, 5·5%; equiv., 255). The chloroform solutions from these experiments yielded a non-homogeneous material [(i) 0·23, (iii) 0·33, (iv) 0·64 g.] which may have contained the oxazine since, by the following ring-opening procedure,[1] it gave *N*-phenylacetylanthranilic acid. The material was heated at 50° for 1 min. with trichloroacetic acid (2 g.) and sulphuric acid (0·8 ml.); the solution was poured into water, and the precipitate was

[14] Bogert, Gortner, and Amend, *J. Amer. Chem. Soc.*, 1911, **33**, 952.
[15] Diesbach, Gross, and Tschannen, *Helv. Chim. Acta*, 1951, **34**, 1050.

recrystallised from aqueous ethanol. The specimens of *N*-phenylacetylanthranilic acid so obtained [(i) 0·10, (iii) 0·11, (iv) 0·40 g.] had m. p.s 182·5—187° and m. p.s 186—189° when mixed with the acid above.

Propylidenephthalide [(i), (ii) 3·48 g.] and 2-butyrylbenzoic acid [(iii), (iv) 3·84 g.] both gave *N*-butyrylanthranilic acid [(i) 2·89, (ii) 2·76, (iii) 3·24, (iv) 3·11 g.], m. p. 117·5—118·5°; after recrystallisation from ethanol–water (1 : 1) it had m. p. 118·5—119° (Found: equiv., 209. Calc. for $C_{10}H_{11}ON{\cdot}CO_2H$: equiv., 207). Pictet and Du Parc [16] record m. p. 117°. In these experiments the acidic aqueous solution was concentrated, made alkaline, and distilled in steam; aqueous sodium hydroxide was added to the distillate which was then shaken with benzoyl chloride (0·7 ml.) and thrice extracted with ether. The latter yielded specimens of *N*-propylbenzamide [(i) 0·15, (ii) 0·19, (iii) 0·11, (iv) 0·25 g.] which, after recrystallisation from benzene–light petroleum (b. p. 60—80°), had m. p.s in the range 77—83° alone and when mixed with an authentic specimen of m. p. 83°.

N-Phenylacetylanthranilic acid (5·0 g.) and acetic anhydride (15 ml.) were heated under reflux for 30 min.; after distillation of acetic acid and acetic anhydride, finally under reduced pressure, the product was recrystallised from anhydrous methanol; it yielded 2-*benzyl*-6-*oxo*-4 : 5-*benz*-1 : 3-*oxazine* (3·35 g.), needles, m. p. 90·5° (Found: C, 75·8; H, 4·8; N, 5·75. $C_{19}H_{11}O_2N$ requires C, 75·9; H, 4·65; N, 5·9%). This oxazine (1·18 g., 0·0050 mole) was subjected to the Schmidt reaction procedure on ½ scale (sodium azide omitted), and gave *N*-phenylacetylanthranilic acid (1·23 g.), m. p. 182°; after recrystallisation from aqueous ethanol it (0·96 g.) had m. p. 187·5—188° alone and when mixed with an authentic specimen.

The oxazine (0·80 g.) was heated on a steam-bath with acetic acid–water (4 : 1; 8 ml.) for 30 min. On cooling, there separated *N*-phenylacetylanthranilic acid (0·81 g.), m. p. and mixed m. p. 188°. A similar experiment with ethanol–water (4 : 1) gave this acid (0·76 g.) having m. p. and mixed m. p. 188·5—189°.

N-Butyrylanthranilic acid, on being heated with acetic anhydride according to Zentmeyer and Wagner,[4] was converted into 6-oxo-2-propyl-4 : 5-benz-1 : 3-oxazine, which after two recrystallisations from methanol had m. p. 58·5° (the above authors record m. p. 59—60°). This oxazine (0·95 g., 0·0050 mole) was subjected to the Schmidt procedure on ½ scale (sodium azide omitted); there was obtained *N*-butyrylanthranilic acid (0·91 g.) having m. p. 113·5° and mixed m. p. 115°.

This oxazine (0·95 g.) was treated as above with aqueous acetic acid (9·5 ml.). No solid separated from the cold solution, but addition of water gave a precipitate of *N*-butyrylanthranilic acid (0·96 g.) which had m. p. and mixed m. p. 116°. The oxazine (0·80 g.) was heated as above with aqueous ethanol (8 ml.); the cold solution was thrice extracted with chloroform, which yielded *N*-butyrylanthranilic acid (0·82 g.) m. p. 112° and mixed m. p. 114·5—115°.

2-*p*-Chlorophenyl-6-oxo-4 : 5-benz-1 : 3-oxazine (1·00 g.) was treated as above with aqueous acetic acid (10 ml.). After cooling, the mixture was filtered, yielding a product (0·92 g.), m. p. 177—182°, which was dissolved in chloroform (30 ml.); the solution was twice extracted with aqueous sodium hydrogen carbonate, washed with water, and dried. It yielded the oxazine (0·73 g.), m. p. and mixed m. p. 188·5°. From the sodium hydrogen carbonate solution a solid (m. p. > 300°) separated which on treatment with dilute hydrochloric acid gave a product (0·14 g.) having m. p. 207° (Zentmeyer and Wagner [4] record m. p. 204—205° for *N*-*p*-chlorobenzoylanthranilic acid).

This oxazine (1·00 g.) was heated as above with aqueous ethanol (10 ml.); it (0·96 g.) was recovered, having m. p. and mixed m. p. 189·5°.

Three Schmidt reactions were carried out by the procedure above, except that, at the end of the reaction, the chloroform and the sulphuric acid layers were separated. The latter was washed with chloroform (2 × 25 ml.), and the combined chloroform solutions were filtered and evaporated; in each instance they gave no residue. The sulphuric acid layer was poured on ice.

(1) 2-*p*-Chlorobenzoylbenzoic acid yielded material (5·30 g.), m. p. 182—184°, which was stirred with chloroform (150 ml.); the latter was filtered, twice washed with aqueous sodium hydrogen carbonate, dried, and evaporated; it gave a product (0·36 g.) which on recrystallisation from ethanol yielded 2-*p*-chlorophenyl-6-oxo-4 : 5-benz-1 : 3-oxazine (0·23 g.), m. p. 189·5°. The chloroform-insoluble material (4·18 g.) and that obtained on acidification of the sodium hydrogen carbonate solution (0·56 g.) after two recrystallisations from aqueous ethanol gave *N*-*p*-chlorobenzoylanthranilic acid (3·46 g.), m. p. 207·5°.

[16] Pictet and Du Parc, *Ber.*, 1887, **20**, 3421.

2-*p*-Chlorophenyl-6-oxo-4 : 5-benz-1 : 3-oxazine (2·00 g.) was dissolved in sulphuric acid (6 ml.), and the solution was kept at 30° for 30 min., and then poured on ice; the solid which separated was recrystallised from aqueous ethanol, yielding *N*-*p*-chlorobenzoylanthranilic acid (1·68 g.), m. p. 207·5°.

(2) The diluted sulphuric acid layer from the reaction with 2-mesitoylbenzoic acid [(i)—(iii) 2·68 g., 0·0100 mole] was shaken with chloroform (50 ml.), and the whole was filtered. The chloroform solution was separated, washed with aqueous sodium hydrogen carbonate, and with water, and dried. It yielded 2-mesityl-6-oxo-4 : 5-benz-1 : 3-oxazine [(i) 0·77, (ii) 0·60, (iii) 0·70 g., from ethanol], m. p. 134—136° and, on further recrystallisation, m. p. 139°, mixed m. p. 139·5—140°. The material which was insoluble in dilute sulphuric acid and in chloroform was recrystallised from aqueous dioxan; in two experiments it yielded *N*-mesitylphthalimide [(i) 0·61, (iii) 0·45 g.] having m. p. 178—179°, and on further recrystallisation m. p. 180° alone and when mixed with an authentic specimen of the same m. p.; in (ii) it gave *N*-mesitylphthalamidic acid (0·62 g.), m. p. 191·5—192·5° (decomp.) raised by further recrystallisation to 193·5—194° (decomp.).

(3) 2-Butyrylbenzoic acid yielded *N*-butyrylanthranilic acid (3·19 g.), m. p. 115°.

N-*m*-Nitrophenylphthalamidic acid [(i), (ii) 0·36 g., m.p. 206·5° (decomp.); Meyer and Lüders [17] record m. p. 201° (decomp.)], sulphuric acid (98%, 15 ml.), and chloroform (35 ml.) were stirred for 2 hr. at 30°, and the mixture was then treated as in the Schmidt procedure. The following were obtained. Insoluble in chloroform and dilute sulphuric acid: unchanged *N*-*m*-nitrophenylphthalamidic acid [(i), (ii) 0·14 g.], m. p. 206° (decomp.). From chloroform: material [(i) 0·11, (ii) 0·10 g.] which, on crystallisation from ethanol, yielded *N*-*m*-nitrophenylphthalimide, m. p. 246° and m. p. 246·5° when mixed with an authentic specimen of m. p. 246·5—247°. From the acidic aqueous solution: *m*-nitroaniline [(i), (ii) 0·04 g.], m. p. 107—111°, and, on recrystallisation from water, m. p. and mixed m. p. 111·5—112°.

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[17] Meyer and Lüders, *Annalen*, 1918, **415**, 48.

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323. *The Determination of Small Concentrations of Alcohols.*

By V. S. GRIFFITHS and D. I. STOCK.

An electrometric method of determining small concentrations (less than 0·05% w/v) of methyl, ethyl, *iso*propyl, *n*-propyl, and *iso*pentyl alcohol is described.

THE literature contains a variety of methods for determination of ethyl alcohol,[1,2] but these were not considered suitable for work in hand where a rapid method suitable for adaptation to automatic control was required; consequently an electrometric method has been developed. This involved oxidation of the alcohol by an excess of standard potassium dichromate solution, followed by electrometric back-titration of the excess with ferrous ammonium sulphate. The choice of electrodes presented some difficulty. In a preliminary investigation an irreversible electrode couple was selected, with no liquid junction.[3] The cell consisted of a piece of tungsten and a piece of platinum sealed separately into the flask in which the reaction was to take place. The advantage of this system is that the cell has a low resistance, and that the E.M.F. falls sharply to a value close to zero at the end-point. This arises from the fact that platinum assumes the reversible (redox) potential of the solution during the titration of dichromate with a ferrous salt, whereas the potential of tungsten is nearly unchanged. Thus at the end-point the potential of the platinum electrode falls sharply to that characteristic of the Fe^{3+}–Fe^{2+} system, the overall E.M.F.

[1] Nicholls, "The Determination of Alcohol," *Royal Inst. Chem. Monograph*, 1947.
[2] Reid and Salmon, *Analyst*, 1955, **80**, 704.
[3] Furman, *et al.*, *J. Amer. Chem. Soc.*, 1919, **41**, 1337; 1928, **50**, 273, 277.

becoming virtually zero. While this arrangement does give a true end-point, the actual potential is far from reproducible, and the method was abandoned. Attention was then turned towards the use of the glass electrode as a reference standard in redox titrations.[4,5] The cell used can be written :

| Ag | $AgNO_3$ (0·1M-aqueous solution) | Glass membrane | Redox system in heavily buffered acid solution | Pt |

In this system both metal electrodes are reversible, and the reference electrode is connected to the controlling electrode through a glass membrane. The procedure normally adopted in carrying out a redox titration of this kind is to use two reversible electrodes, one as a reference standard and the other as a " reaction-controlled " electrode, the two being connected by means of a salt bridge. While this arrangement is usually satisfactory for analytical laboratory work, it is not well suited to automatic control because of the difficulties introduced by the presence of the liquid junction. It is true that the potential across the glass membrane is controlled by the pH of the redox system, but in the presence of a large amount of sulphuric acid this pH is sensibly constant and does not in any case change rapidly at the end-point, so that the potential assumed by the platinum is the sole factor governing the E.M.F. of the cell. The electrode system inside the glass membrane (Ag | $AgNO_3$, 0·1M) was selected because the whole cell thus constituted was found to have an E.M.F. which reversed in direction at the end-point, giving a change in E.M.F. of approximately 350—400 mv for an added volume of titrant corresponding to a change of less than 0·0005% in the alcohol content of the sample. However, experiment showed that it is possible to use a normal commercial glass electrode (as used for pH determinations) in place of the above system, when the E.M.F. change is of the same order, though not showing the reversal of direction at the end-point.

The method is not absolute, and it is necessary to construct a calibration curve, by using standard solutions of alcohol and a carefully standardised technique.

Experimental

A series of ethyl alcohol–water standards, made up at concentrations 0·05, 0·036, 0·02, 0·01, 0·005, 0·002, and 0·001% w/v, was used for the construction of the calibration curves. The alcohol solution (5·0 ml.) was added to 0·025N-potassium dichromate solution (5·0 ml.), and concentrated sulphuric acid (5·0 ml.) added with stirring. The solution becomes hot, thus aiding the oxidation of the alcohol. 5 min. after addition of the sulphuric acid the solution was titrated with 0·00625N-ferrous ammonium sulphate, E.M.F. readings being taken after each addition. The oxidation is to some extent time-dependent, so that it is necessary to standardise the experimental technique and to treat both standard solutions and unknown in the same way. The curve relating volume of ferrous ammonium sulphate solution to alcohol content was very nearly linear between 0·05% and 0·01%, becoming slightly convex towards the volume axis at lower concentrations. Reproducibility was excellent, duplicate determinations agreeing consistently to within better than 0·05 ml. of ferrous ammonium sulphate solution. From about 0·05% to 0·01% this would correspond to about $\pm$0·00015% of alcohol in the original sample. The maximum displacement of any mean titration value from a smooth calibration curve was 0·1 ml., this being at an alcohol concentration of 0·005%, where such a volume corresponds to 0·0002% alcohol on the original. The method thus affords a means of determining the concentration of ethyl alcohol in aqueous solution down to at least 0·0005% (5 p.p.m.) with an estimated error of not more than $\pm$2 p.p.m. There does not appear to be any reference in the literature to the electrometric determination of alcohol, but Reid and Salmon [3] have recently described a colorimetric method, using ceric ammonium nitrate as oxidising agent. They observe that an exact timing of the oxidation period is essential, and report an accuracy of $\pm$20 p.p.m., their lowest concentration being 0·01% w/v. The oxidation-time factor in the method described here is only $\pm$0·1 ml. of ferrous ammonium sulphate/min. at 5 min., but it is obviously preferable to keep the oxidation time as constant as possible.

During the work a number of membranes was used, and whilst the absolute potential values

[4] Lykken and Tuemmler, *Ind. Eng. Chem. Analyt.*, 1942, **14**, 67.
[5] Wynd, *Ann. Missouri Bot. Garden*, 1935, **22**, 861.

were not always the same for a given alcohol concentration, the magnitude of the change at the end-point was always of the same order.

It was also found possible to determine the concentrations of methyl, *iso*- and *n*-propyl, and *iso*pentyl alcohol in aqueous solutions by this method, and it is capable of further extensions.

This method has been tested on a commercial ethyl alcohol stripping column. Samples from the column had been analysed by distillation into standard dichromate solution and sulphuric acid, followed by the addition of potassium iodide and back-titration with standard thiosulphate. The agreement was within 0·005% overall (on a total of about 0·02% w/v), but the results indicated that the distillation method tended to cause a variable and indeterminate loss of alcohol.

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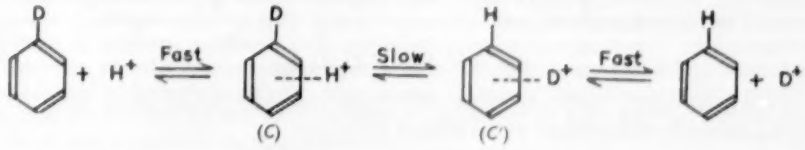
324. *The Mechanism of Aromatic Sulphonation and Desulphonation in Aqueous Sulphuric Acid.*

By V. GOLD and D. P. N. SATCHELL.

The sulphonation of benzene by aqueous sulphuric acid (77·5—87·6 wt. %) has been studied kinetically as a homogeneous reaction by application of an isotope dilution technique. These measurements and earlier data on sulphonation and desulphonation in aqueous acid are shown to be compatible with the scheme shown in (1).

WE have recently found [1] that the rate of replacement of nuclear deuterium atoms in aromatic molecules by protium derived from acidic solvents is proportional to h_0 (where $-\log h_0 = H_0 =$ Hammett's acidity function [2]). The reaction is one which involves electrophilic aromatic substitution by hydrogen. We have argued that the observed kinetics are best explained on the basis of a mechanism in which the electrophilic reagent is involved in a rapid pre-equilibrium. The particular formulation which we favour is as follows:



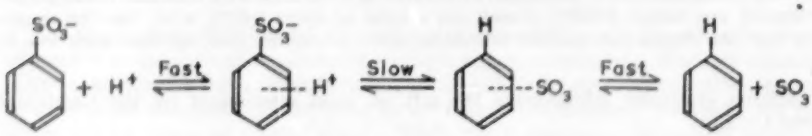
where C and C' are non-classical structures analogous to Mulliken's "outer complexes." [3]

If such a mechanism is involved in one case of electrophilic substitution by hydrogen, then it seems likely that broadly similar mechanisms operate in other cases. This idea is supported by the example of replacement of trimethylsilyl,[4] for which the rate has, in fact, been found to be proportional to h_0, and perhaps also by those of demercuration [5] and deiodination.[6] In the last example the acidity functions of the solutions used are not known, but the rates increase with the acidity of the solvent considerably faster than does the stoicheiometric concentration of strong acid used and such a steep concentration dependence is also usually characteristic of the acidity function in mixtures of strong acids with other solvents.

These considerations are of interest in connection with the mechanism of desulphonation,

[1] (*a*) Gold and Satchell, *Nature*, 1955, **176**, 602; *J.*, 1955, 3609, (*b*) *J.*, 1955, 3619, (*c*) *J.*, 1955, **3622**.
[2] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940.
[3] Mulliken, *J. Phys. Chem.*, 1952, **56**, 801.
[4] (*a*) Eaborn, *J.*, 1953, 3148; (*b*) Benkeser and Krysiak, *J. Amer. Chem. Soc.*, 1954, **76**, 6353.
[5] Corwin and Naylor, *ibid.*, 1947, **69**, 1004; Kaufman and Corwin, *ibid.*, 1955, **77**, 6280.
[6] Gold and Whittaker, *J.*, 1951, 1184.

this being another reaction of the same general type. The analogy between hydrogen exchange and desulphonation is particularly close in view of the similarity of the reaction media (aqueous sulphuric and other acids) involved in the two cases. If we assume that the mechanisms are analogous, then, since the sulphonate ion is likely to be much more reactive towards electrophilic attack than the undissociated sulphonic acid, the mechanism of desulphonation can be represented as follows :



(1)

The net reaction (negligible reversal being assumed) is :

$$H^+ + Ar{\cdot}SO_3^- \longrightarrow ArH + SO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The rate of desulphonation (v_{DS}) is then given by

$$v_{DS} = k'_{-}h_{-}[Ar{\cdot}SO_3^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(square brackets implying concentration), and the first-order rate coefficient (k_{DS}) by

$$k_{DS} = v_{DS}/[Ar{\cdot}SO_3H]_{stoich.} = k'_{-}h_{-}[Ar{\cdot}SO_3^-]/[ArSO_3H]_{stoich.} \quad . \quad . \quad (4)$$

[In these expressions h_- (where $-\log h_- = H_-$) must be used [2] rather than h_0, since the base involved in the pre-equilibrium is negatively charged. However, the distinction between h_0 and h_- may in practice be relatively unimportant.[7]] The experimentally observable form of the relation between reaction velocity and acidity will depend on the extent to which the sulphonic acid is converted into the sulphonate ion in the media in question. The extent of this conversion is governed by equation (5) and therefore depends on the values

$$[Ar{\cdot}SO_3H]/[Ar{\cdot}SO_3^-] = h_-/K^a_{Ar{\cdot}SO_3H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

of h_- and of the dissociation constant $K^a_{Ar{\cdot}SO_3H}$ of the sulphonic acid. According to equation (4), if $[Ar{\cdot}SO_3^-] \gg [Ar{\cdot}SO_3H]$ and therefore $[Ar{\cdot}SO_3^-] \sim [Ar{\cdot}SO_3H]_{stoich.}$, then k_{DS} should be proportional to h_-, or

$$v_{DS} = k'_{-}h_{-}[Ar{\cdot}SO_3H]_{stoich.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

If, on the other hand, $[Ar{\cdot}SO_3H] \gg [Ar{\cdot}SO_3^-]$ and therefore $[Ar{\cdot}SO_3H] \sim [Ar{\cdot}SO_3H]_{stoich.}$ then k_{DS} should be independent of the solvent acidity, or

$$v_{DS} = k_{-}[Ar{\cdot}SO_3H]_{stoich.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $k_- = k'_- \cdot K^a_{Ar{\cdot}SO_3H}$.

Aromatic sulphonic acids are fairly strong acids but, on the basis of structural analogies, would be expected to be appreciably weaker than sulphuric acid. The rate of desulphonation might therefore be expected to follow h_- (or h_0) in sulphuric acid solutions of low acidity, but to increase less steeply when h_0 becomes comparable in magnitude with $K^a_{Ar{\cdot}SO_3H}$. This expectation appears to be realised in practice. Crafts's work [8] on the desulphonation of *p*-xylenesulphonic acid in aqueous hydrochloric acid at 140° shows that the rate follows h_0 over a range of values [$H_0 = -0{\cdot}4$ to $-2{\cdot}4$ (at 25°)], it being assumed that h_0 at 140° is proportional to h_0 at 25° (Fig. 1). Some other data in the literature concerning desulphonation [9,10] relate to sulphuric acid as solvent and to much higher acidities. In agreement with expectation, the increase in reaction velocity with solvent acidity is less steep in these

[7] Brand, Horning, and Thornley, *J.*, 1952, 1374.
[8] Crafts, *Bull. Soc. chim. France*, 1907, **1**, 917.
[9] Pinnow, *Z. Electrochem.*, 1915, **21**, 380; 1917, **23**, 243.
[10] Lantz, *Bull. Soc. chim. France*, 1935, **2**, 2092.

media, and the results can be quantitatively reconciled with the proposed mechanism by assuming reasonable values ($K^a_{Ar\cdot SO_3H} \sim 10^3$ for quinolsulphonic acid) for the dissociation constants of the sulphonic acids concerned. The experimental evidence is therefore compatible with a mechanism analogous to that which we have advanced for hydrogen exchange, involving a rapid acid–base pre-equilibrium, the actual species undergoing substitution being the sulphonate ion.

The rate of desulphonation is related to that of sulphonation through the corresponding equilibrium constant K. If the sulphonate ion is involved in the way suggested, and v_{DS} is given by equation (6) or (7) as

$$v_{DS} = k_-[Ar\cdot SO_3H] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

then, since

$$K = \frac{k_+^\circ}{k_-^\circ} = \frac{(Ar\cdot SO_3H)}{(ArH)(SO_3)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

(where $k_+^\circ/k_-^\circ = k_+ f_{Ar\cdot SO_3H}/k_- f_{SO_3} \cdot f_{ArH}$)

$$v_S = k_+[ArH][SO_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

or

$$v_S/[ArH] = k_S = k_+[SO_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

(In these expressions parentheses imply activities and the f's represent activity coefficients.)

It therefore follows, from the proposed mechanism for desulphonation, that the first-order rate constants for sulphonation (in excess of acid) will be proportional to the concentration of SO_3 present and, from the principle of microscopic reversibility, that SO_3 will be the only sulphonating agent operating.

The rate coefficients k_+ and k_- will be subject to medium effects, which can be represented by the Brönsted–Bjerrum equation :

$$k_- = k_-^\circ f_{Ar\cdot SO_3H}/f_X$$

$$k_+ = k_+^\circ f_{SO_3} f_{ArH}/f_X$$

where f_X is the activity coefficient of the transition state of the reaction. The magnitude of these medium effects cannot be predicted from existing data, but the fact that recognisable proportionality with species concentrations has been found for the rates of reactions in aqueous sulphuric acid media of varying composition [11] encouraged us to examine the rate of aromatic sulphonation in this solvent as a function of acid concentration. It was hoped to discover in this way whether the conclusion, based on a consideration of our proposed mechanism for the desulphonation reaction, that sulphonation involves attack on the aromatic molecule by SO_3, is tenable.

Cowdrey and Davies [12] were the first to attempt a correlation between sulphonation velocity and acid concentration in terms of the concentrations of the chemical species present in sulphuric acid–water mixtures. In the absence, at that time, of information on the chemical composition of such mixtures, these authors made certain simplifying assumptions about the chemical equilibria present in these media. The most serious of these, as far as the conclusions about sulphonation in aqueous sulphuric acid are concerned, was their implicit assumption that the concentration of the species H_2SO_4 would remain constant throughout the concentration range 92—99% sulphuric acid. Although it is now clear that this particular assumption is incorrect,[13] it is not possible to allow for it entirely by reference to the recent data on the composition of aqueous sulphuric acid [14] because of the high temperature used by Cowdrey and Davies. An unambiguous analysis of their rate measurements does not seem possible at present.

[11] *E.g.*, Lowen, Murray, and Williams, *J.*, 1950, 3318; Bonner, Bowyer, and Williams, *J.*, 1952, 3274.
[11] Cowdrey and Davies, *J.*, 1949, 1871.
[12] Young, *Record of Chem. Progress*, Spring issue, 1951, 81.
[14] Deno and Taft, *J. Amer. Chem. Soc.*, 1954, **76**, 244.

The measurements now reported relate to the rate of sulphonation of benzene in dilute homogeneous solution in aqueous sulphuric acid over the concentration range 77·5—87·6 wt. %. In addition to their interest in the present connection, the data amplify a previous statement [15] that sulphonation did not interfere with our kinetic measurements of deuterium exchange between benzene and aqueous sulphuric acid, although in agreement with earlier work on heterogeneous hydrogen exchange between benzene and aqueous sulphuric acid, the rate of sulphonation has been found to increase more rapidly than the rate of exchange as the concentration of acid is raised.

FIG. 1. *Desulphonation of p-xylenesulphonic acid in aqueous hydrochloric acid at 140° (Crafts).*

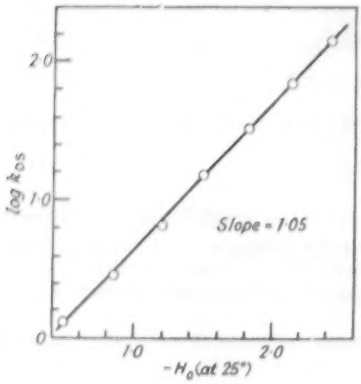
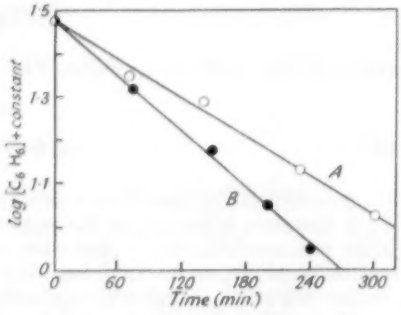


FIG. 2. *Sulphonation of benzene in excess of aqueous sulphuric acid. Specimen first-order plots.*



(*a*) 15·43M-H_2SO_4. (*b*) 15·71M-H_2SO_4.

EXPERIMENTAL

General Procedure.—Benzene was dissolved in various sulphuric acid–water mixtures. After various periods of time the unchanged hydrocarbon was equilibrated with a definite amount of a suitable C_6H_5D–C_6H_6 mixture. The composition of the resulting mixture was determined by infrared analysis [15] from which the amount of C_6H_6 remaining in the acid was calculated. We found it impossible with our equipment to analyse C_6H_5D–C_6H_6 mixtures accurately by using a band characteristic of the species C_6H_6, as there is none sufficiently free from overlap with bands found in C_6H_5D. Further, benzene is sparingly soluble in aqueous sulphuric acid, and it is also necessary to add a sufficient amount of the C_6H_5D–C_6H_6 mixture to permit phase separation. For these reasons the accuracy of the analytical method is not high. The quoted rate constants have limits of error of the order of ±20%. From the point of view of the general dependence of sulphonation rate on acid composition, the large range of velocities measured makes this error in the absolute values of the individual rate constants of minor importance.

Detailed Procedure.—Measured samples (~0·30 ml.) of "AnalaR" benzene were dissolved in samples (400 ml.) of a given sulphuric acid–water mixture contained in flasks fitted with ground-glass stoppers and having an additional sealing of Apiezon "Q compound." Four or five samples were used for each acid–water mixture, and altogether eight different acid–water mixtures were studied covering the range 77·5—87·6 wt. % (13·43—16·09M).

After an appropriate period in a thermostat at 25°, a flask was opened, the acid mixture diluted with water, and a measured amount (~1·0 ml.) of a C_6H_5D–C_6H_6 mixture of known composition added to its contents, which, after re-sealing of the flask, were agitated for 15 min. The benzene and acid phases were now separated, and the benzene stored over a little calcium chloride and barium carbonate in a sealed flask (5 ml.) and then subjected to isotopic analysis.[15]

Appreciable desulphonation was shown to be absent in the following manner: (i) the addition of samples of calcium benzenesulphonate to similar acid–water mixtures showed no benzene to be formed even after long periods of time; (ii) the kinetics of sulphonation showed no evidence of the presence of residual benzene remaining in equilibrium when the reaction was followed over many half-lives.

Specimen first-order plots are shown in Fig. 2. The rate constants are collected below.

Stoich. concn. of H_2SO_4 (M) ...	13·43	13·87	14·61	14·68	15·10	15·43	15·71	16·09
$10^5 k_s$ (sec.$^{-1}$)	0·026	0·075	0·65	1·13	2·5	5·7	8·3	32

The monodeuterobenzene was prepared as previously described.[15] The strengths of the acid–water mixtures were determined by titration.

Discussion

In order to test the rate equation (11) for sulphonation in aqueous sulphuric acid, it is necessary to express the unknown concentration of SO_3 in terms of known concentrations of other species. By considering the equilibrium

$$SO_3 + H_2O \rightleftharpoons H_2SO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

(with an equilibrium constant K_H) we obtain

$$[SO_3] = [H_2SO_4] f_{H_2SO_4} / K_H (H_2O) f_{SO_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

and hence, from (11),

$$k_S = k_+ [H_2SO_4] f_{H_2SO_4} / K_H (H_2O) f_{SO_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Values for the activity of water in aqueous sulphuric acid can be derived from data in the literature, as previously reviewed.[14,16] In the evaluation of $[H_2SO_4]$, two approaches seem possible. In the first place, we may refer to the concentrations of various chemical species in the acids as derived from direct measurements of Raman spectra.[13] Unfortunately, the existing measurements are comparatively inaccurate for $[H_2SO_4]$ in the region of interest in the present study. We have, therefore, used instead the indirectly obtained mass-law equation :

$$[H_3O^+][HSO_4^-]/[H_2O][H_2SO_4] = 50 \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

which appears to lead to a consistent picture of the composition of sulphuric acid above 75% by weight.[14] If equation (14) represents the rate of sulphonation of benzene, the rate constant k_S should be proportional to $[H_2SO_4]/[(H_2O)$, provided that the ratio $f_{H_2SO_4}/f_{SO_3}$ stays reasonably constant. Because of the large range of rates covered, the concentration dependence of the velocity of sulphonation is more clearly tested by logarithmic graphs. Curve I (Fig. 3) is a graph of {log $[H_2SO_4]/(H_2O)$ + Constant} against the weight percentage of sulphuric acid in the solvent, and the circles represent the experimental points of (log k_S + Constant), the additive constants in these two quantities being adjusted so as to make the functions meet at the lowest point. The discrepancy between the experimental points and curve I is clearly appreciable and, if the proposed mechanism and manner of calculation of $[H_2SO_4]/(H_2O)$ are correct, it implies that the term log $(f_{H_2SO_4}/f_{SO_3})$ increases by ~0·7 unit on going from 77·5 to 87·6% acid.

Nothing is known at present about the activity coefficients of H_2SO_4 and SO_3 in aqueous sulphuric acid. However, we may perhaps take the ratio of the activity coefficients of another pair of solutes whose molecular formulæ differ only by the elements of water, as a rough guide to the direction in which $f_{H_2SO_4}/f_{SO_3}$ may be expected to vary. As one of us has shown,[17] the difference between the acidity function J_o and certain approximations to J_o may be used to evaluate certain combinations of activity coefficients in aqueous sulphuric acid. In particular, the result [17] that :

$$J_o - J_o' = \log (f_B f_{R^+} / f_{BH^+} f_{ROH}) \approx -\log (f_{ROH_2^+} / f_{R^+}) \quad . \quad . \quad . \quad (16)$$

where J_o' is a certain approximation to J_o, is of interest in the present connection, since R^+ and ROH_2^+ are two solutes related to each other in the required manner. [For the

[15] Bryce-Smith, Gold, and Satchell, *J.*, 1954, 2743.
[16] Gold and Hawes, *J.*, 1951, 2102.
[17] Gold, *J.*, 1955, 1263.

acidity range considered R = $(NO_2{\cdot}C_6H_4)_3C$.] Two independent sets of experimental data [18,19] are available which give the values of J_0 and, according to both, $f_{ROH_2}{}^+/f_{R^+}$ increases as the proportion of sulphuric acid in the solvent rises. The discrepancy between the experimental points and curve I could thus appear to be in the right direction. Unfortunately, the two sets of data show a marked and puzzling quantitative disagreement over the particular range of interest. According to the data of Williams *et al.*,[11] log $f_{ROH_2}{}^+/f_{R^+}$ increases by about 0·7 unit between 77·5 and 81·6% H_2SO_4, but according to those of Deno *et al.*[19] the increase amounts to only 0·1 unit. It is tempting to choose the set of data which gives the difference of 0·7 unit, since this is precisely the change we wish to ascribe to $f_{H_2SO_4}/f_{SO_3}$, but at the moment there does not appear to be any other reason for preferring this set, and in any case an exact parallelism between $f_{H_2SO_4}/f_{SO_3}$ and $f_{ROH_2}{}^+/f_{R^+}$ is hardly to be expected. Curve II (Fig. 3), which is seen to pass through the experimental points, is, however, a plot, based on Williams's data,[18] of {log $[H_2SO_4]/(SO_3) + J_0' - J_0$ + Constant}, and, although we do not wish to over-stress the significance of this close fit, it seems to us that the experimental data are compatible with the mechanism outlined.

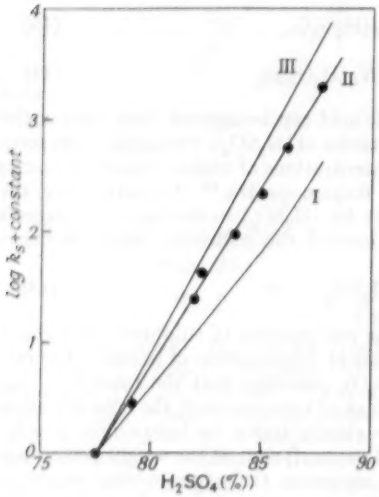


FIG. 3. *Dependence of sulphonation velocity for benzene on acid composition.*

I, Y = log {$[H_2SO_4]/(H_2O)$} + Constant.
II, Y = log {$[H_2SO_4]/(H_2O)$} + $J_0' - J_0$ + Constant.
III, Y = log {$h_0[H_2SO_4]/(H_2O)$} + Constant.
●, Experimental points (log k_S + Constant).

We shall now examine whether the data are sufficiently diagnostic to rule out other mechanisms for sulphonation.

If the attacking entity were SO_3H^+, the rate constant of sulphonation would be given by:

$$v_S/[ArH] = k_S = k_+'[SO_3H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

which is analogous to (11). If we assume that the concentrations of SO_3 and SO_3H^+ are related to each other through Hammett's acidity function, the equation (17) becomes

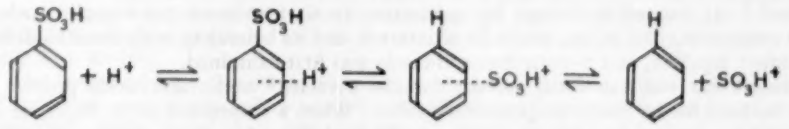
$$k_S = k_+'[SO_3]h_0/K^a_{SO_3H^+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

where $K^a_{SO_3H^+}$ is the acidity constant of SO_3H^+. Substituting for $[SO_3]$ from (13), we find

$$k_S = \frac{k'_+}{K^a_{SO_3H^+}K_{II}} \cdot h_0 \cdot \frac{[H_2SO_4]}{(H_2O)} \cdot \frac{f_{H_2SO_4}}{f_{SO_3}} \quad . \quad . \quad . \quad . \quad . \quad (19)$$

[18] Murray and Williams, *J.*, 1950, 3322; Williams and Bevan, *Chem. and Ind.*, 1955, 171.
[19] Deno, Jaruzelski, and Schriesheim, *J. Amer. Chem. Soc.*, 1955, **77**, 3044; cf. *idem*, *J. Org. Chem.*, 1954, **19**, 155.

The function $h_0[H_2SO_4]/(H_2O)$ can now be calculated as before. Its logarithm (+ Constant) is plotted in curve III (Fig. 3), and is seen to increase more steeply with acid concentration than the experimental points. However, the divergence of these points from curve III is no more marked than their divergence from curve I; but, as we have seen, it seems likely that $f_{H_2SO_4}/f_{SO_4}$ increases with sulphuric acid concentration and this will accentuate the disagreement for curve III, whereas it reduces it for curve I. For this reason equation (14) appears preferable to equation (19). The mechanism on which equation (19) is based (involving attack by SO_3H^+) could be written, together with its



(20)

reversal, as in (20). This mechanism requires the velocity of desulphonation in 77·5—87·6% sulphuric acid to be proportional to h_0, since in this region one expects $[Ar{\cdot}SO_3H]$ to be $\gg [Ar{\cdot}SO_3^-]$. The experimental data do not entirely rule this out. A further requirement of the mechanism is that the rate of electrophilic attack on the sulphonic acid is more important than the attack on the sulphonate ion which is present in much lower concentration. This again is conceivable but seems unlikely, on intuitive grounds, over the particular range of acidities. In solutions of higher acidity (such as oleum) it may be expected that the mechanism (20) would assume greater importance since, with increasing acidity, the concentration of sulphonate ions will progressively fall and that of SO_3H^+ ions will rise. Accordingly, we do not regard our conclusions as incompatible with those of Brand and Horning,[20] according to whom SO_3H^+ is the active sulphonating species in oleum.

A number of other mechanisms for sulphonation have recently been considered. According to these, the sulphonation reaction and its reversal are to be written

$$H_3SO_4^+ + ArH \rightleftharpoons Ar{\cdot}SO_3H + H_3O^+ \quad . \quad . \quad . \quad . \quad . \quad (21)$$

$$S_2O_6 + ArH \rightleftharpoons Ar{\cdot}SO_3H + SO_3 \quad . \quad . \quad . \quad . \quad . \quad (22)$$

$$H_2S_2O_7 + ArH \rightleftharpoons Ar{\cdot}SO_3H + H_2SO_4 \quad . \quad . \quad . \quad . \quad (23)$$

$$HS_2O_7^- + ArH \rightleftharpoons Ar{\cdot}SO_3^- + H_2SO_4 \quad . \quad . \quad . \quad . \quad (24)$$

Schemes (21) and (22) seem to be incompatible with experimental results on desulphonation in requiring the rate to be proportional to the concentration of either H_3O^+ or SO_3. Schemes (23) and (24) predict a concentration-dependence for sulphonation which, over the range studied by us, is almost indistinguishable from schemes (1) and (20) respectively, and we have no direct experimental grounds for rejecting them. Our reason for not putting them forward as probable alternative mechanisms is entirely based on the postulated analogy between desulphonation and dedeuteration, discussed on p. 1936, and would be void if this analogy should later be found to be incorrect. For the same reason we have not explicitly considered the termolecular mechanisms discussed by Cowdrey and Davies.[12]

UNIVERSITY OF LONDON, KING'S COLLEGE, STRAND, W.C.2. [*Received, November 23rd*, 1955.

[20] Brand, *J.*, 1950, 997; Brand and Horning, *J.*, 1952, 3922.

325. *Some Heterocyclic Quaternary Dichloroiodides.*

By Frances M. Hamer.

By treatment at a low temperature with sulphuryl chloride in acetic anhydride, six heterocyclic quaternary ethiodides were converted into crystalline dichloroiodides. One of these was converted into a quaternary salt by use of zinc in acetic acid and one by use of carbon tetrachloride.

Sulphuryl chloride can function in various ways, according to the conditions of reaction.[1] It proved a powerful chlorinating agent for alkylpyrroles, whereby aldehydes and acids were synthesised.[2] It seemed as though its application to six-membered heterocyclic nuclei, having a reactive methyl group, might be of interest, and its behaviour with the ethiodides of quinaldine, lepidine, and 2-methylbenzothiazole was first examined.

Whereas ether was the usual solvent for the pyrroles,[2] acetic anhydride proved a suitable medium for heterocyclic quaternary salts. When a suspension of an ethiodide in that solvent was treated at a low temperature with a solution of an equimolecular quantity of sulphuryl chloride, it quickly dissolved and a new salt crystallised. The crude products were unstable but, after being washed, could be recrystallised from acetic acid and, when dry, could be kept without apparent deterioration.

In each of the three instances named, analyses showed that two chlorine atoms had been added. The methyl group was not involved since quinoline ethiodide and benzothiazole methiodide behaved similarly. When 2-iodoquinoline ethiodide was treated with two molecular equivalents of sulphuryl chloride, two chlorine atoms were added and, besides, chlorine replaced iodine in the 2-position. Negative results, which were obtained when the starting points were quinaldine ethochloride and 2-methylbenzothiazole ethotoluene-*p*-sulphonate, indicated that the iodine atom was essential. So it was concluded that the products were dichloroiodides.

Attempts to prepare the dichloroiodide of a 4 : 4′-cyanine and of a thiacarbocyanine similarly in acetic anhydride were unsuccessful.

Perhalides of tetra-alkylammonium salts have been prepared by interaction of a halogen, in alcohol or acetic acid, with a quaternary salt;[3] tetrachloroiodides of various organic bases have been prepared by the action of iodine and chlorine on a hydrochloric acid solution of the bases.[4]

That the present crystalline compounds are perhalides is confirmed by the ease of removal of halogen. Thus the compound prepared from 2-methylbenzothiazole ethiodide was quickly decolorised by zinc in acetic acid but double salt formation made isolation of quaternary salt difficult. However, excess of sodium hydroxide was used to remove the zinc salt; the resultant methylene base was extracted and was acidified to give a salt.

In decomposing perhalides, the halogen atom which remains attached to the cation is the lightest in the molecule.[5] As carbon tetrachloride dissolves halogens, it was chosen in studying the dissociation of polyhalides.[6] The present salt from quinaldine ethiodide was shaken hot with water and carbon tetrachloride; at first iodine was readily removed, but protracted treatment was necessary for its complete removal; the salt in the aqueous layer was quinaldine ethochloride.

Experimental.

1-Ethyl-2-methylquinolinium Dichloroiodide.—A suspension of powdered quinaldine ethiodide (2·99 g., 1 mol.) in acetic anhydride (3 c.c.) was cooled with ice–salt, and a cooled solution of sulphuryl chloride (1 mol.) in acetic anhydride (3 c.c.) was added in one lot. A brown colour developed, the solid dissolved, and the colour became lighter. On stirring, crystals separated. They were filtered off (smell of sulphur dioxide) and washed twice with acetic anhydride and five times with absolute ether, and dried in a vacuum-desiccator. On recrystallisation from

[1] Brown, *Ind. Eng. Chem.*, 1944, **36**, 785.
[2] Fischer, Sturm, and Friedrich, *Annalen*, 1928, **461**, 249.
[3] Chattaway and Hoyle, *J.*, 1923, **123**, 654.
[4] Chattaway and Garton, *J.*, 1924, **125**, 183.
[5] Sidgwick, "The Chemical Elements and their Compounds," Oxford Univ. Press, 1950, Vol. II, p. 1195.
[6] Cremer and Duncan, *J.*, 1931, 2243.

acetic acid (20 c.c. per g.), the 37% yield dropped to 33%. The yellow *dichloroiodide*, both before and after recrystallisation, had m. p. 99—100°, with previous yellowing (Found: C, 39·1; H, 4·05; O, 0; N, 3·8; Cl, 19·45; I, 34·5; S, 0. $C_{12}H_{14}NCl_2I$ requires C, 38·95; H, 3·8; N, 3·8; Cl, 19·15; I, 34·3%). When twice the amount of acetic anhydride was used, the yields were 23% and 20%. When the sulphuryl chloride was added during 3 min., inoculation was necessary to start crystallisation, and the yield of washed salt was only 7%.

1-*Ethyl*-4-*methylquinolinium Dichloroiodide*.—Lepidine ethiodide similarly gave the lemon-yellow *dichloroiodide*, m. p. 114° (decomp.) (46% after two crystallisations from acetic acid) (Found: C, 39·2; H, 4·15; N, 3·5; Cl, 18·95; I, 34·2%).

3-*Ethyl*-2-*methylbenzothiazolium Dichloroiodide*.—2-Methylbenzothiazole ethiodide similarly gave the bright yellow *ethodichloroiodide*, m. p. 85—86°, the yield being 32% after recrystallisation from acetic acid (Found: C, 31·95; H, 3·4; I, 33·85. $C_{10}H_{12}NCl_2IS$ requires C, 31·95; H, 3·2; I, 33·75%).

1-*Ethylquinolinium Dichloroiodide*.—From quinoline ethiodide (2·85 g.) and sulphuryl chloride the yield of pale yellow washed *perhalide* was 42%. Twice recrystallised from acetic acid (yield 32%), it had m. p. 100° (Found: C, 36·95; H, 3·65; N, 3·8; Cl, 19·75; I, 35·7. $C_{11}H_{12}NCl_2I$ requires C, 37·1; H, 3·4; N, 3·95; Cl, 19·9; I, 35·65%).

3-*Methylbenzothiazolium Dichloroiodide*.—From benzothiazole methiodide (2·77 g.), the yield of *perhalide* was 63%, and after two recrystallisations from acetic acid 48%. The pale yellow crystals had m. p. 139° (decomp.), with previous yellowing (Found: C, 27·8; H, 2·6; N, 3·9; Cl, 19·95; I, 36·9; S, 9·05. $C_8H_8NCl_2IS$ requires C, 27·6; H, 2·3; N, 4·0; Cl, 20·35; I, 36·45; S, 9·2%).

2-*Chloro*-1-*ethylquinolinium Dichloroiodide*.—2-Iodoquinoline ethiodide (2·06 g., 1 mol.) and sulphuryl chloride (2 mols.) in acetic anhydride (6 c.c.) similarly gave a crude salt (109%) which was crystallised from acetic acid, and washed three times with acetic acid and five times with ether, yielding the pale yellow *perhalide* (57%), m. p. 124° (Found: C, 33·95; H, 3·2; N, 3·5; Cl, 27·6; I, 32·7. $C_{11}H_{11}NCl_2I$ requires C, 33·85; H, 2·85; N, 3·6; Cl, 27·25; I, 32·5%).

Breakdown of 3-*Ethyl*-2-*methylbenzothiazolium Dichloroiodide*.—The dichloroiodide (0·75 g., 1 mol.), suspended in acetic acid (15 c.c.), was heated with zinc dust (8 atoms) on the water-bath, with stirring, for 3 min. After filtration hot, the filtrate and washings were treated, with cooling, with sodium hydroxide (20 g.) in water (100 c.c.) and extracted with chloroform. The extract was washed once with water, then extracted with 17% hydrochloric acid (6 × 4 c.c.). The acid extracts were evaporated to dryness on the water-bath and in a vacuum-desiccator. The product (42% yield) was recrystallised from ethanol and then anhydrous acetone (21% yield; as for 2-methylbenzothiazole ethochloride, recrystallised similarly). When the product was heated, it and its mixture with 2-methylbenzothiazole ethochloride behaved like that salt, partly melting about 150° and frothing up to about 180°. When boiled with pyridine and ethyl orthoformate, it gave the same colour as did 2-methylbenzothiazole ethochloride.

Breakdown of 1-*Ethyl*-2-*methylquinolinium Dichloroiodide*.—This dichloroiodide (0·37 g.) was shaken with carbon tetrachloride (40 c.c.) and water (40 c.c.), on the water-bath. The aqueous layer became orange and the lower layer deep pink. After cooling, the latter was filtered and the treatment was repeated with fresh solvent (40 c.c.), which became slightly less intensely coloured. The third extract was paler but even the last of eight such extracts was pink. The last extract was left in contact with the aqueous layer for 48 hr. during which its colour deepened. After three further extractions with carbon tetrachloride (3 × 80 c.c.) on the water-bath with stirring for 15 min. both layers were colourless. The final aqueous layer was taken to dryness on the water-bath and in a vacuum-desiccator but the product (100% yield) was brown. It was recrystallised from ethanol (charcoal) by addition of anhydrous acetone. The 29% yield of colourless crystals was of the same order as the yield obtained when quinaldine ethochloride was similarly recrystallised. They were free from iodine, although the crude product gave a faint positive test (CS_2–H_2SO_4). The recrystallised salt, quinaldine ethochloride, and their mixture all decomposed at 236° (darkening *ca.* 170°). When heated with pyridine and ethyl orthoformate, the salt gave a blue colour, as did quinaldine ethochloride, thus confirming the identity.

Analyses were carried out in the microanalytical laboratory (Mr. F. H. Oliver and his staff) of this Department. I thank Kodak Ltd. for financing the work, Dr. R. P. Linstead, F.R.S., for affording facilities, and Prof. E. A. Braude for his interest.

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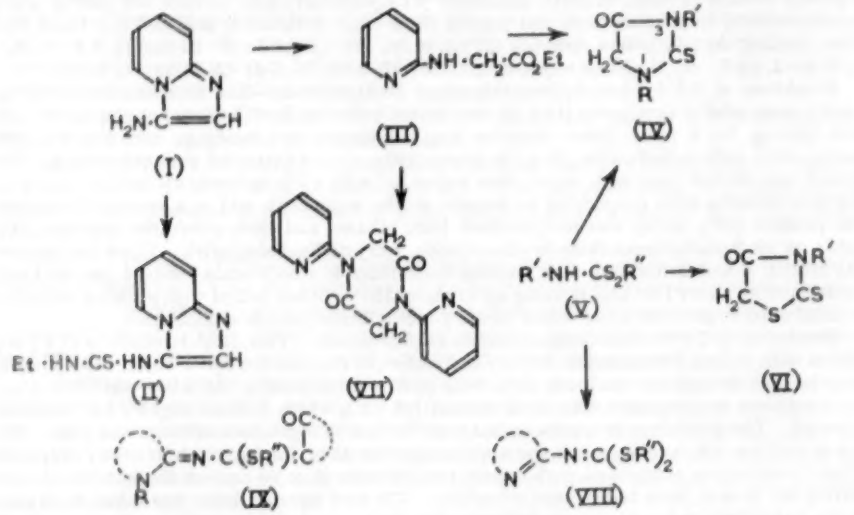
326. *Heterocyclyl-rhodanines and -2-thiohydantoins.*

By Edward B. Knott.

Ethyl *N*-2-pyridylaminoacetate has been converted into a series of 3-substituted 1-2′-pyridyl-2-thiohydantoins. *N*-Pyridyl-, *N*-quinolyl-, and *N*-thiazolyl-dithiocarbamic esters have been condensed with *N*-substituted glycines, glycine esters, or glycine nitriles to give 3-pyridyl-, 3-quinolyl-, and 3-thiazolyl-2-thiohydantoins, or have been cyclized to the 3-substituted rhodanines.

The formation of 1 : 3-disubstituted 2-thiohydantoins (IV) is usually brought about by the condensation of an *iso*thiocyanate [1] or a *N*-substituted dithiocarbamic ester [2] with a *N*-substituted glycine, glycine ester, or glycine nitrile.[3] Substituted rhodanines (VI) are usually obtained by cyclizing the carboxymethyl ester of a *N*-substituted dithiocarbamic acid.[4]

The difficulty of obtaining glycines, dithiocarbamates, or *iso*thiocyanates carrying heterocyclic residues on the nitrogen atom no doubt accounts for the absence in the literature of preparations of 2-thiohydantoins or rhodanines derivable from them. Tien and Hunsberger [5] recently reported the preparation of *N*-3-pyridylglycine, and Bristow, Charlton, Peak, and Short [6] described the synthesis of *N*-2-pyridylglycine nitrile. The latter, unlike *N*-alkylglycine nitriles, is unsuitable for the preparation of 2-thiohydantoins since, as found by Bristow *et al.*,[6] it behaves like the isomeric glyoxaline (I), reacting with ethyl *iso*thiocyanate to give what is probably the thiourea (II). It is readily



hydrolyzed to ethyl *N*-2-pyridylaminoacetate (III) which, on distillation, is partly converted into the diketopiperazine (VII). The aminoacetate (III) condenses normally with *iso*thiocyanates or dithiocarbamic esters to give 3-substituted 1-2′-pyridyl-2-thiohydantoins (IV; R = 2-C_5H_4N). In a similar manner ethyl *N*-(6-methyl-2-pyridyl)-aminoacetate was prepared and converted into 3-substituted 1-(6-methyl-2-pyridyl)-2-thiohydantoins.

It was then found that 2-, 3-, and 4-aminopyridines, 3-aminoquinoline (but not the

[1] Neumark and Stelzner, *Ber.*, 1891, **24**, 3285.
[2] Wheeler, Nicolet, and Johnson, *Amer. Chem. J.*, 1911, **46**, 456.
[3] Delépine, *Bull. Soc. chim. France*, 1903, **29**, 1198; Cook and Cox, *J.*, 1949, 2343.
[4] Holmberg, *J. prakt. Chem.*, 1910, **81**, 455.
[5] Tien and Hunsberger, *Chem. and Ind.*, 1955, 119.
[6] Bristow, Charlton, Peak, and Short, *J.*, 1954, 616.

2-isomer), and 2-aminothiazole (but not 2-aminobenzothiazole) condensed readily with carbon disulphide and triethylamine at room temperature to give high yields of the corresponding 1-substituted triethylammonium dithiocarbamates (V; R″ = Et_3NH). This reaction has recently been published by Fairfull and Peak.[7] The alkyl, preferably methyl, esters of these dithiocarbamic acids (V; R″ = Me), with *N*-substituted glycines, glycine esters, or glycine nitriles, readily yielded 1-substituted 2-thiohydantoins with the heterocyclic residue at position 3. Fusion of the dithiocarbamate (V; R″ = Me, R′ = 2- or 3-pyridyl) at 140° caused the evolution of methanethiol and the formation of a tar from the 2-isomer, but of 3-pyridyl *iso*thiocyanate from the 3-isomer. This *iso*thiocyanate is a high-boiling liquid (cf. Fairfull *et al.*[7]) and it therefore seems likely that the 2-pyridyl analogue obtained by the latter authors as a brick-red solid with m. p. 110—111° is a polymer.

Condensation of sodium chloroacetate with triethylammonium dithiocarbamates from heterocyclic compounds, followed by acidification of the solution of the salt of the carboxymethyl ester (V; R″ = $CH_2{\cdot}CO_2H$) so formed, leads in some cases directly to the rhodanine derivatives (VI). In other cases the carboxymethyl ester was isolated and subsequently cyclized to these products (VI), either by fusion or by treatment with acetic anhydride.

These methyl dithiocarbamates are, like thioamides, soluble in sodium hydroxide and on treatment with methyl iodide in alcoholic sodium ethoxide give the dimethyl dithiocarbimidates (VIII). These bases are then readily quaternized and converted into azadimethin*mero*cyanines (IX) substituted in the chain by methylthio-groups.

Experimental

Ethyl N-2-*Pyridylaminoacetate* (III).—*N*-2-Pyridylaminoacetonitrile (20 g.) (Bristow *et al.*[6]) was added to a cooled solution of concentrated sulphuric acid (20 c.c.) in ethanol (100 c.c.). The sulphate, which was precipitated, gradually dissolved under reflux. After 2 hours' boiling the solution was poured on ice (200 g.), the acid was neutralized with solid sodium hydrogen carbonate, and the oil extracted with ether. The dried ethereal solution gave 20·8 g. (82%) of *ester*, b. p. 156—160°/13·5 mm., on distillation (Found: C, 59·7; H, 6·6; N, 15·6. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·65; N, 15·55%), which solidified to asbestos-like needles at 5°. The residue from the distillation (1·8 g.; soft yellow needles, m. p. 252°, from acetic acid) is believed to be 2 : 5-*dioxo*-1 : 4-*di*-2′-*pyridylpiperazine* (VII) (Found: C, 63·0; H, 4·65; N, 20·7. $C_{14}H_{12}O_2N_4$ requires C, 62·7; H, 4·5; N, 20·9%).

Ethyl N-6-*methyl*-2-*pyridylaminoacetate* was obtained similarly in 48% yield based on 2-amino-6-methylpyridine, as a colourless oil, b. p. 158—162°/12 mm. (Found: C, 62·0; H, 7·3; N, 14·6. $C_{10}H_{14}O_2N_2$ requires C, 61·85; H, 7·2; N, 14·45%).

N-*Ethyl*-N′-[*pyridino*(1 : 2-*a*)*glyoxalin*-5-*yl*]*thiourea* (II).—*N*-2-Pyridylaminoacetonitrile (13·3 g.) and ethyl *iso*thiocyanate (8·8 c.c.) were fused together on a steam-bath for 5 min. The melt had then solidified. It (12·2 g., 55%) formed colourless needles, m. p. 206°, from ethanol (Found: C, 54·5; H, 5·1; N, 25·4; S, 14·7. $C_{10}H_{12}N_4S$ requires C, 54·5; H, 5·45; N, 25·5; S, 14·55%).

Triethylammonium N-2-*Pyridyldithiocarbamate* (V; R′ = 2-C_5H_4N, R″ = NEt_3).—2-Aminopyridine (18·8 g.), carbon disulphide (12 c.c.), and triethylamine (30 c.c.) were warmed to give a clear solution. Two phases separated rapidly and the whole was shaken at room temperature for 1½ hr. The whole had then solidified. The mass was ground with ether, washed with ether, and air-dried. It (49·0 g., 90·5%) formed lemon-yellow plates, m. p. 84—85° (Fairfull *et al.*[7] give 82% yield and m. p. 88—89°) (Found: C, 53·2; H, 7·6; N, 15·2; S, 23·7. Calc. for $C_{12}H_{21}N_3S_2$: C, 53·1; H, 7·75; N, 15·5; S, 23·6%).

It afforded the *ethoxycarbonylmethyl ester* (V; R′ = 2-C_5H_4N, R″ = $EtO_2C{\cdot}CH_2$), pale yellow aggregates, m. p. 88—89°, from methanol (Found: C, 46·6; H, 4·7; N, 11·1; S, 25·2. $C_{10}H_{12}O_2N_2S_2$ requires C, 46·9; H, 4·7; N, 10·95; S, 25·0%), and the methyl ester (V; R′ = 2-C_5H_4N, R″ = Me), pale lemon spears, m. p. 91°, from ethanol (lit., m. p. 88—89°) (Found: C, 45·9; H, 4·2; N, 14·9; S, 34·7. Calc. for $C_7H_8N_2S_2$: C, 45·7; H, 4·35; N, 15·2; S, 34·8%). The latter ester, on fusion at 145°, evolved methanethiol smoothly but the residue, an orange-coloured tar with the odour of benzothiazole and a sharp tang, could not be distilled without decomposition. The *ethyl ester* (V; R′ = 2-C_5H_4N, R″ = Et), obtained in 71% yield, formed lemon-yellow needles, m. p. 64°, from propan-2-ol (Found: N, 14·0; S, 32·3. $C_8H_{10}N_2S_2$ requires N, 14·15; S, 32·3%). 1-(N-2-*Pyridylthiocarbamoyl*)*piperidine* was obtained

[7] Fairfull and Peak, *J.*, 1955, 796.

in 96% yield by keeping the methyl ester (9·2 g.) and piperidine (5 c.c.) in methanol (20 c.c.) for 15 hr. and then refluxing the mixture for 1 hr. It formed white flakes, m. p. 112—113°, from *cyclo*hexane (Found: C, 59·9; H, 6·95; N, 18·9; S, 14·7. $C_{11}H_{15}N_3S$ requires C, 59·7; H, 6·8; N, 19·0; S, 14·5%).

Triethylammonium *N*-3-pyridyldithiocarbamate, obtained as for the 2-isomer in 42% yield, formed yellow prisms, m. p. 87° (effervescence), from ether (lit.[7] 92% yield, m. p. 85—86°) (Found: C, 52·9; H, 7·5; N, 15·4; S, 23·6. Calc. for $C_{12}H_{21}N_3S_2$: C, 53·1; H, 7·75; N, 15·5; S, 23·6%). The derived methyl ester, white flakes, m. p. 135—136° (lit.,[7] m. p. 133—135°) (Found: N, 15·2; S, 34·7. Calc. for $C_7H_8N_2S_2$: N, 15·2; S, 34·8%) (5·0 g.), was fused at 145°/14 mm. Methanethiol was evolved, and then 3-pyridyl *iso*thiocyanate (3·3 g., 89·2%) distilled at 104°. The almost colourless oil, with the odour of benzothiazole and a sharp tang, had b. p. 228°/765 mm. (lit.,[7] b. p. 231—233°) (Found: C, 52·8; H, 3·1; N, 20·4; S, 23·7. Calc. for $C_6H_4N_2S$: C, 52·95; H, 2·95; N, 20·6; S, 23·55%).

Triethylammonium N-4-Pyridyldithiocarbamate.—4-Aminopyridine (4·8 g.) was dissolved in hot pyridine (30 c.c.), then cooled to room temperature, and carbon disulphide (3·3 c.c.) and triethylamine (8 c.c.) were added. After 3—4 hr. crystals separated and next morning ether (100 c.c.) was added and the solid was washed with cold ethanol. The *salt* (6·9 g., 51%) formed orange flakes, m. p. 141°, from methanol–ether (Found: C, 53·3; H, 7·9; N, 15·2; S, 23·8%), and afforded the *methyl ester* in 74% yield as pale yellow prisms, m. p. 142—144°, from ethanol (Found: C, 46·0; H, 4·65; N, 15·0; S, 34·95. $C_7H_8N_2S_2$ requires C, 45·7; H, 4·35; N, 15·2; S, 34·8%).

Triethylammonium N-6-methyl-2-pyridyldithiocarbamate (85%) was obtained as for the above but 24 hours' shaking was necessary for solidification. It formed lemon-yellow aggregates, m. p. 76°, from methanol–ether (Found: N, 14·45; S, 22·55. $C_{13}H_{23}N_3S_2$ requires N, 14·75; S, 22·5%). The *methyl ester*, obtained in 71% yield, formed pale yellow plates, m. p. 89—90°, from methanol (Found: N, 14·1; S, 32·45. $C_8H_{10}N_2S_2$ requires N, 14·15; S, 32·35%).

Methyl N-4-Methyl-2-pyridyldithiocarbamate.—2-Amino-4-methylpyridine (54·0 g.), carbon disulphide (33 c.c.), triethylamine (80 c.c.), and dioxan (20 c.c.) were refluxed together to dissolve the amine. Two phases then separated and the whole was shaken at room temperature for 24 hr. The orange tar was washed with ether, and methanol (100 c.c.) was added followed by methyl iodide (30 c.c.). An exothermic reaction set in which was controlled by cooling. After 1 hr. water was run into the solution, to give 75·6 g. (76%) of the ester, which formed pale yellow needles, m. p. 101—102°, from methanol (Found: N, 14·3; S, 32·0%).

Bistriethylammonium Salt of 2:6-Bis(dithiocarboxyamino)pyridine.—2:6-Diaminopyridine (10·9 g.) was dissolved in pyridine (40 c.c.), and triethylamine (33 c.c.) and carbon disulphide (14 c.c.) were added. Two phases separated after 5 min. and the whole was then shaken at room temperature for 16 hr. The solid was washed with ether, and then ethanol. The *bis-dithiocarbamate* (39·7 g., 86%) formed orange crystals, m. p. 112°, from methanol–ether (Found: N, 14·95; S, 27·8. $C_{19}H_{37}N_5S_4$ requires N, 15·1; S, 27·65%). The derived *dimethyl ester* (78% yield) formed buff crystals, m. p. 132—133°, from ethanol (Found: N, 14·5; S, 44·6. $C_9H_{11}N_3S_4$ requires N, 14·5; S, 44·3%).

Triethylammonium N-3-Quinolyldithiocarbamate.—3-Aminoquinoline (5·0 g.), carbon disulphide (2·2 c.c.), and triethylamine (5·5 c.c.) were kept in dioxan (10 c.c.) at room temperature for 20 hr. The solid cake of *salt* (98%) formed pale yellow prisms, m. p. 89°, from ethanol–ether (Found: N, 12·95; S, 19·65. $C_{14}H_{23}N_3S_2$ requires N, 13·1; S, 19·95%) and gave a *methyl ester* (87%), pale yellow needles, m. p. 137—138° (from ethanol) (Found: C, 56·2; H, 4·3; N, 11·85; S, 27·3. $C_{11}H_{10}N_2S_2$ requires C, 56·4; H, 4·3; N, 11·95; S, 27·35%).

Triethylammonium N-2-thiazolyldithiocarbamate, with pyridine as solvent, was obtained in 60% yield as yellow flakes, m. p. 142° (lit.,[7] m. p. 141—142°). The *methyl ester* formed straw-coloured needles, m. p. 175—176°, from ethanol (lit.,[7] m. p. 184—185°) (Found: C, 31·35; H, 3·2; N, 14·75; S, 50·0. Calc. for $C_5H_6N_2S_2$: C, 31·6; H, 3·2; N, 14·75; S, 50·5%).

2-Aminobenzothiazole, 2-aminoquinoline, and 2-amino-4:6-dimethylpyrimidine could not be brought into reaction with carbon disulphide and triethylamine.

3-Ethyl-1-2′-pyridyl-2-thiohydantoin (IV; R = 2-C_5H_4N; R′ = Et).- Ethyl *N*-2-pyridylaminoacetate (18·0 g.) and ethyl *iso*thiocyanate (13·3 g.) were fused together at 135° for 5 hr. The melt solidified when chilled. The solid *thiohydantoin* (14·6 g., 44%) formed greenish flakes, m. p. 107°, from propan-2-ol or *cyclo*hexane (Found: C, 54·3; H, 5·15; N, 18·85; S, 14·75. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 4·95; N, 19·0; S, 14·45%).

1-Phenyl-3-2′-pyridyl-2-thiohydantoin (IV; R = Ph, R′ = 2-C_5H_4N).—Ethyl *N*-phenylaminoacetate (1·0 g.) and methyl *N*-2-pyridyldithiocarbamate (1·0 g.) were fused together at

150° for 15 min. The melt solidified and the *product* (0·7 g., 47%) formed cream-coloured needles, m. p. 190°, from ethanol (Found: C, 62·3; H, 4·3; N, 15·55; S, 12·1. $C_{14}H_{11}ON_3S$ requires C, 62·5; H, 4·1; N, 15·65; S, 11·9%).

1 : 3-*Di*-(6-*methyl*-2-*pyridyl*)-2-*thiohydantoin*.—Ethyl *N*-(6-methyl-2-pyridyl)aminoacetate (10·0 g.) and methyl *N*-(6-methyl-2-pyridyl)dithiocarbamate (10·2 g.) were fused together at 145° for 2 hr. The melt solidified after 1½ hr. The cooled solid was ground under ethanol to give 11·85 g. (77·0%) of yellow crystals. It was extracted with boiling ethanol (5 × 50 c.c.), leaving 9·3 g. of undissolved residue, which formed white crystals, m. p. 220—222° from benzene in which it was sparingly soluble (Found: C, 60·25; H, 4·65; N, 18·6; S, 10·8. $C_{15}H_{14}ON_4S$ requires C, 60·45; H, 4·7; N, 18·8; S, 10·75%). The ethanol extract, on concentration to 100 c.c., gave yellow flakes (2·0 g.) when chilled, m. p. 189—190°, after a further recrystallization from benzene (Found: C, 60·75; H, 4·9; N, 19·0; S, 11·05%). Both *compounds* behave as 2-*thiohydantoins* in dye condensations. The nature of the isomerism has not been investigated. The thiohydantoins given in the Table were obtained by similar methods.

1 : 3-*Disubstituted* 2-*thiohydantoins* (IV).

R′	Time (hr.) *	Yield (%) (solvent) †	M. p.	Formula	Required (%) C	H	N	S	Found (%) C	H	N	S
R = 2-pyridyl												
Me	7	47 (E)	141°	$C_9H_9ON_3S$	52·7	4·3	20·1	15·5	52·2	4·35	20·3	15·45
Ph	7	56 (A) [a]	186	$C_{14}H_{11}ON_3S$	62·3	4·2	15·85	11·1	62·5	4·1	15·65	11·9
Allyl	2	39 (M) [b]	62	$C_{11}H_{11}ON_3S$	57·0	4·8	17·8	13·8	56·6	4·7	18·0	13·75
*cyclo*Hexyl	7	40 (E)	174	$C_{14}H_{17}ON_3S$	60·8	6·25	14·9	11·8	61·0	6·2	15·25	11·65
Benzyl	5	63 (M) [c]	115	$C_{15}H_{13}ON_3S$	63·8	5·0	15·1	11·2	63·6	4·6	14·85	11·3
n-Heptyl	7 [f]	70 (E) [d]	70	$C_{13}H_{21}ON_3S$	61·5	7·3	14·45	11·2	61·8	7·2	14·45	11·0
2-Pyridyl	2 [g]	67 (E) [e]	173	$C_{13}H_{10}ON_4S$	58·0	3·9	20·65	11·9	57·8	3·7	20·75	11·85
3-Pyridyl	2 [h]	72 (E) [e]	170—171	$C_{13}H_{10}ON_4S$	—	—	20·55	12·05	—	—	20·75	11·85
6-Methyl-2-pyridyl	2 [h]	73 (E)	146—147	$C_{14}H_{12}ON_4S$	59·4	4·35	19·65	11·4	59·2	4·25	19·85	11·25
4-Methyl-2-pyridyl	1½	57 (E) [f]	151	$C_{14}H_{12}ON_4S$	59·5	4·5	19·65	11·25	59·2	4·25	19·85	11·25
3-Quinolyl	½	62 (E) [b,c]	204	$C_{17}H_{12}ON_4S$	63·6	3·95	17·1	10·2	63·75	3·75	17·5	10·0
R = 6-methyl-2-pyridyl												
Et	6	29 (P)	85	$C_{11}H_{13}ON_3S$	56·3	5·7	17·9	13·7	56·15	5·5	17·85	13·6

* At 150° unless otherwise stated.

† E = ethanol, A = acetic acid, M = methanol, P = propan-2-ol. The products are white needles unless otherwise stated.

[a] Black. [b] Straw-coloured. [c] Pale green. [d] Flakes. [e] Buff-coloured. [f] 135°. [g] 145°. [h] 140°.

1-*Ethyl*-3-2′-*pyridyl*-2-*thiohydantoin* (IV; R = Et, R′ = 2-C_5H_4N).—Ethylaminoacetonitrile (4·2 g.) and methyl *N*-2-pyridyldithiocarbamate (9·2 g.) were heated together on a steam-bath for 1 hr. Methanethiol was evolved and an orange-coloured tar remained. 5*N*-Hydrochloric acid (30 c.c.) was added and the clear orange-coloured solution was heated for a further 30 min. Water (100 c.c.) was added and the solution was basified with ammonia, to give orange-coloured grains (10·2 g.) which were ground in a little ethanol and filtered (5·6 g.). The product was dissolved in benzene (50 c.c.) and chilled overnight. The white needles, m. p. 135—136°, which separated were discarded and the benzene solution was concentrated to 25 c.c. The addition of light petroleum (b. p. 60—80°) gave a gummy *thiohydantoin* which yielded 2·2 g. (20%) of flat, buff needles, m. p. 132°, after crystallization from ethanol and then from benzene (Found: C, 54·5; H, 4·95; N, 18·8; S, 14·7. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 4·95; N, 19·0; S, 14·4%).

1-*Methyl*-3-2′-*thiazolyl*-2-*thiohydantoin* (IV; R = Me, R′ = 2-C_3H_2NS).—To a solution of potassium hydroxide (5·6 g.) in water (25 c.c.) was added sarcosine hydrochloride (6·3 g.), followed by methyl *N*-2-thiazolyldithiocarbamate (9·5 g.) and ethanol (50 c.c.). The mixture was heated for 20 hr. Water (100 c.c.) was added and the solid filtered off. The filtrate was acidified with dilute acetic acid, the small amount of tar was filtered off, and the filtrate was concentrated to 100 c.c. An orange-coloured tar separated on chilling, which crystallized completely in 3 days. From ethanol the *thiohydantoin* (1·9 g., 18%) formed pink needles, m. p. 133° (Found: C, 39·55; H, 3·45; N, 19·7; S, 30·25. $C_7H_7ON_3S_2$ requires C, 39·4; H, 3·3; N, 19·7; S, 30·1%).

1-*Ethyl*-3-2′-*thiazolyl*-2-*thiohydantoin* was obtained similarly in 28% yield from *N*-ethylglycine hydrochloride, and formed pink needles, m. p. 176—177°, from ethanol (Found: C, 41·95; H, 4·1; N, 18·5; S, 28·25. $C_8H_9ON_3S_2$ requires C, 42·25; H, 4·0; N, 18·5; S, 28·45%).

3-2′-*Pyridyl*-2-*thiothiazolid*-4-*one* (VI, R′ = 2-C_5H_4N).—Triethylammonium *N*-2-pyridyldithiocarbamate (5·4 g.) was dissolved in water (30 c.c.), and a solution of sodium chloroacetate (2·4 g.) in water (10 c.c.) was added at 20°. The solution was kept for 20 hr. and acidified with acetic acid. The resulting solid (3·2 g., 70%) formed orange-coloured aggregates, m. p. 133° (effervescence), from ethanol. It is *carboxymethyl* N-2′-*pyridyldithiocarbamate* (V; R′ = 2-C_5H_4N, R″ = $HO_2C{\cdot}CH_2$) (Found: C, 42·1; H, 3·75; N, 12·05; S, 28·3. $C_8H_8O_2N_2S_2$ requires C, 42·1; H, 3·5; N, 12·3; S, 28·1%). The ester (4·6 g.) and acetic anhydride (40 c.c.) were heated together for 1 hr. on a steam-bath, and the solvent was removed. The reddish tar was dissolved in propan-2-ol (25 c.c.) and kept for several weeks. The pale yellow *thiazolidone* (1·2 g., 28·5%) which had then separated formed rosettes of straw-coloured needles, m. p. 77°, from propan-2-ol (Found: N, 13·1; S, 30·35. $C_8H_6ON_2S_2$ requires N, 13·35; S, 30·5%).

5-1′-*Ethoxyethylidene*-3-2′-*pyridyl*-2-*thiothiazolid*-4-*one*.—By the same procedure as for the above cyclization, but in the presence of ethyl orthoacetate (10 c.c.), the required *rhodanine* was obtained in 49% yield as rose-coloured flakes, m. p. 137—138°, from *cyclo*hexane, then from benzene (Found: C, 51·1; H, 4·6; N, 9·95; S, 23·05. $C_{12}H_{12}O_2N_2S_2$ requires C, 51·4; H, 4·3; N, 10·0; S, 22·9%).

3-(6-*Methyl*-2-*pyridyl*)-2-*thiothiazolid*-4-*one* (VI; R′ = 6-Me-2-C_5H_3N).—Triethylammonium *N*-(6-methyl-2-pyridyl)dithiocarbamate (28·5 g.) and sodium chloroacetate (13·0 g.) were dissolved in water (100 c.c.) at 35°. When the solution was allowed to cool some solid separated. After 2 hr. the solution was filtered and acidified with dilute acetic acid. The thick, yellow meal was washed with water and air-dried. The product (22·5 g., 93%), forming fawn needles, m. p. 125° (effervescence), from ethanol, was *carboxymethyl* N-(6-*methyl*-2-*pyridyl*)*dithiocarbamate* (Found: N, 11·4; S, 26·5. $C_9H_{10}O_2N_2S_2$ requires N, 11·55; S, 26·45%). It was finely ground and heated at 125°/12 mm. The solid slowly fused, with effervescence, to give an orange-coloured tar which then crystallized. This was boiled with methanol (15 c.c.) and chilled, to give 4·8 g. (52%) of the *rhodanine* as pink flakes, m. p. 146—148°, after recrystallization from benzene then from propan-2-ol (Found: C, 48·3; H, 3·65; N, 12·55; S, 28·85. $C_9H_8ON_2S_2$ requires C, 48·25; H, 3·55; N, 12·5; S, 28·55%). The 5-1′-*ethoxyethylidene derivative* formed orange-coloured prisms, m. p. 165—166°, from ethanol (Found: C, 52·8; H, 4·85; N, 9·3; S, 21·7. $C_{13}H_{14}O_2N_2S_2$ requires C, 53·0; H, 4·75; N, 9·55; S, 21·8%).

3-3′-*Pyridyl*-2-*thiothiazolid*-4-*one*.—3-Aminopyridine (5·0 g.), dioxan (5 c.c.) and triethylamine (8 c.c.) were heated together to give a clear solution. Carbon disulphide (3·2 c.c.) was added and the whole was shaken for 2 hr. A solution of sodium chloroacetate (7·0 g.) in water (50 c.c.) was added, the whole was then heated for 10 min. on a steam-bath, and cooled, water (50 c.c.) was added, and the solution was acidified with dilute acetic acid. A tar was deposited which crystallized after several hours. The *rhodanine* (5·2 g., 46%) formed brown needles, m. p. 156—157°, from ethanol (Found: C, 46·1; H, 3·05; N, 13·25; S, 30·45. $C_8H_6ON_2S_2$ require C, 45·7; H, 2·85; N, 13·35; S, 30·5%).

3-4′-*Pyridyl*-2-*thiothiazolid*-4-*one*.—The above procedure, with the 4-pyridyl isomer as starting point, gave an 81% yield, on acidification of the reaction mixture, of *carboxymethyl* N-4′-*pyridyldithiocarbamate*, orange-coloured prisms, m. p. 152—153° (from aqueous acetic acid) (Found: N, 12·3; S, 28·2. $C_8H_8O_2N_2S_2$ requires N, 12·3; S, 28·1%). This cyclized readily in hot acetic anhydride (10 min. on a steam-bath). Decomposition of the reaction mixture with water gave a little tar, the filtrate from which on treatment with solid sodium hydrogen carbonate gave a 65% yield of the *rhodanine*, reddish prisms, m. p. 162—164° (from ethanol) (Found: N, 13·1; S, 30·2. $C_8H_6ON_2S_2$ requires N, 13·35; S, 30·5%).

3-2′-*Thiazolyl*-2-*thiothiazolid*-4-*one*.—Triethylammonium *N*-2′-thiazolyldithiocarbamate (27·7 g.) and sodium chloroacetate (11·6 g.) were dissolved in water (100 c.c.) and ethanol (100 c.c.) at 55°. After 10 min. a mass of yellow needles separated. The solution was allowed to cool and after 1 hr. the sodium salt of carboxymethyl *N*-2-thiazolyldithiocarbamate (23·2 g., 91%) was collected and washed with ethanol. The salt was dissolved in warm water (500 c.c.), and the solution was filtered and acidified with a solution of acetic acid (6 c.c.) in water (50 c.c.). The free *acid* formed pale yellow crystals, m. p. 178—179° (effervesced, solidified, and then melted at 192°), from acetic acid (Found: N, 11·75; S, 41·1. $C_6H_6O_2N_2S_3$ requires N, 11·95; S, 41·0%). The crystals (18 g.) were dissolved in hot acetic anhydride (50 c.c.) during 15 min. on a steam-bath. After 30 min. acetic acid (10 c.c.) was added and water was added with shaking. A thick, pale yellow meal of crystals separated. The *rhodanine* (14·1 g., 85%) formed straw-coloured needles, m. p. 130°, from ethanol (Found: C, 33·2; H, 2·0; N, 12·85; S, 44·6. $C_6H_4ON_2S_3$ requires C, 33·35; H, 1·85; N, 12·95; S, 44·45%). The 5-1′-*ethoxyethylidene*

derivative formed rust-coloured needles, m. p. 118°, from ethanol (Found: C, 41·8; H, 3·8; N, 9·7; S, 33·8. $C_{19}H_{16}O_2N_2S_2$ requires C, 42·0; H, 3·5; N, 9·8; S, 33·6%).

3-3'-Quinolyl-2-thiothiazolid-4-one, obtained in 86% yield by the same procedure as the 3-pyridyl analogue, formed brown needles, m. p. 228° (soft at 215°), from aqueous acetic acid (Found: C, 55·2; H, 3·15; N, 10·7; S, 24·8. $C_{13}H_8ON_2S_2$ requires C, 55·4; H, 3·1; N, 10·8; S, 24·65%).

Dimethyl N-(2-Pyridyl)dithiocarbimidate (cf. VIII).—Methyl *N*-2'-pyridyldithiocarbamate (18·4 g.) was dissolved in a solution of sodium (2·3 g.) in ethanol (50 c.c.) at 22°, then methyl iodide (6·5 c.c.) was added, causing the temperature to rise to 60°. After 20 hr. at 20° water (150 c.c.) was added, the precipitated oil was taken up in ether, and the solution was dried and distilled. The yellow oil (17·4 g., 88%) was collected at 186°/15 mm. (Found: N, 13·9; S, 32·3. $C_8H_{10}N_2S_2$ requires N, 14·1; S, 32·35%).

3-Ethyl-5-[α-(1-ethyl-1 : 2-dihydropyrid-2-ylideneamino)methylthiomethylene]-2-thiothiazolid-4-one (cf. IX).—Dimethyl *N*-2'-pyridyldithiocarbimidate (4·0 g.) and ethyl toluene-*p*-sulphonate (4·1 g.) were fused together on a steam-bath for 1 hr. 3-Ethylrhodanine (3·3 g.), ethanol (20 c.c.), and triethylamine (1·7 c.c.) were added and the whole was refluxed for 30 min. Water (50 c.c.) was added, the mixture was kept at 5° for 20 hr., the aqueous layer was decanted, and the tar was shaken with benzene (10 c.c.) until crystalline. The *dye* was precipitated fully by the addition of light petroleum (25 c.c.) and recrystallized from methanol. It (3·9 g., 57%) formed rust flakes, m. p. 137—138°, from ethanol (Found: N, 12·2; S, 28·2. $C_{14}H_{17}ON_3S_3$ requires N, 12·4; S, 28·3%).

Dimethyl N-(2-thiazolyl)dithiocarbimidate was obtained in 62% yield by the method used for the 2-pyridyl analogue. It could not be distilled without decomposition. It crystallized completely at 0° and formed pale yellow rods, m. p. 22—23°, from light petroleum (b. p. 60—80°) (Found: C, 35·6; H, 4·05; N, 13·5; S, 46·9. $C_6H_8N_2S_3$ requires C, 35·3; H, 3·9; N, 13·75; S, 47·1%). The *ethiodide* was obtained, by refluxing the base and excess of ethyl iodide for 6 hr., as yellow needles, m. p. 147° (from ethanol–ether) (Found: I, 35·2. $C_8H_{13}N_2IS_3$ requires I, 35·3%).

3-Ethyl-5-[α-(3-ethylthiazolin-2-ylideneamino)methylthiomethylene]-2-thiothiazolid-4-one, obtained as the above analogue in 73% yield, formed violet needles, m. p. 124—126°, from ethanol (Found: C, 41·7; H, 4·5; N, 11·85; S, 37·15. $C_{12}H_{15}ON_3S_4$ requires C, 41·75; H, 4·35; N, 12·15; S, 37·1%).

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327. *Steroids and Walden Inversion. Part XXX.* The Epimeric Coprostan-3-ylamines and Cholest-4-en-3-ylamines.*

By C. W. SHOPPEE, D. E. EVANS, H. C. RICHARDS, and G. H. R. SUMMERS.

Cholestan-3-one oxime, on reduction with sodium–ethanol, gives cholestan-3β-ylamine, but on hydrogenation with platinum in acetic acid affords cholestan-3α-ylamine, and on reduction with lithium aluminium hydride yields both epimeric bases.

Coprostan-3-one oxime on reduction with sodium–ethanol, on hydrogenation, and on reduction with lithium aluminium hydride, appears to yield only coprostan-3α-ylamine, also obtained by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate. Coprostan-3β-ylamine was prepared by ammonolysis of coprostan-3α-yl toluene-*p*-sulphonate.

The reduction of cholest-4-en-3-one oxime with sodium–ethanol and lithium aluminium hydride and of cholest-5-en-3-one oxime with lithium aluminium hydride have been examined.

IN connexion with other studies, we have recently established the configuration at $C_{(3)}$ of 3β-cholesterylamine,[1] 3α-cholesterylamine,[2] and cholestan-3α-ylamine;[3] the configuration

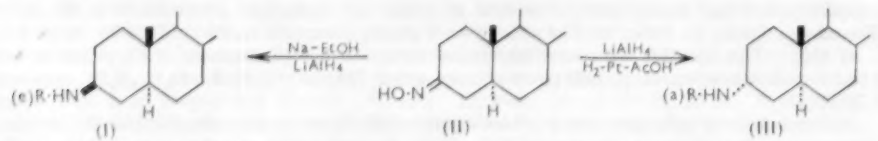
* Part XXIX *J.*, 1956, 1064.

[1] Pierce, Shoppee, and Summers, *J.*, 1955, 690.
[2] Richards, Sly, Shoppee, and Summers, *J.*, 1955, 1054.
Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.

of cholestan-3β-ylamine is already known from the work of Haworth, McKenna, and Powell.[4] We now describe the preparation and establish the configuration at $C_{(3)}$ of the epimeric coprostan-3-ylamines and of the acetyl derivatives of the epimeric cholest-4-en-3-ylamines.

The reduction of oximes of unsymmetrical *cyclo*hexanones with sodium and alcohol gives the equatorial amines, whereas catalytic hydrogenation in acid media generally yields the axial amines.[5, 6, 7] We have found[8] that use of lithium aluminium hydride also affords the axial amines with varying amounts of their equatorial isomerides; a similar observation has been made simultaneously by Labler, Czerny, and Sorm,[9] and more recently by Bannard and McKay.[10] Although steroid 3-ketones should give two geometrically isomeric oximes, one isomeride appears to be formed predominantly or exclusively and the oximes used in the following work appeared to be homogeneous individuals.

Cholestan-3-one oxime (II), on reduction with sodium–ethanol,[11] gave exclusively cholestan-3β-ylamine (I; R = H). Although sodium borohydride in methanol at 20° and 65° was ineffective, use of lithium aluminium hydride afforded cholestan-3α-ylamine (III; R = H), accompanied by an approximately equal quantity[9] of cholestan-3β-ylamine (I; R = H); the bases and their acetyl derivatives were separated chromatographically. Catalytic reduction with platinum in dioxan failed, but proceeded smoothly and rapidly in acetic acid to give exclusively cholestan-3α-ylamine (III; R = H), isolated as the acetyl derivative.



(I) (II) (III)

R = H: m. p. 117°,[9] 120°,[11]
m. p. 118—119°, $[\alpha]_D$ +29° †
R = Ac: m. p. 243°, [α] +12°,[3]
m. p. 246°,[4]
m. p. 245°, $[\alpha]_D$ +12° †

R = H: m. p. 88°,[9]
m. p. 87—88°, $[\alpha]_D$ +27° †
R = Ac: m. p. 216°, $[\alpha]_D$ +33°,[16]
m. p. 217°, $[\alpha]_D$ +36° †

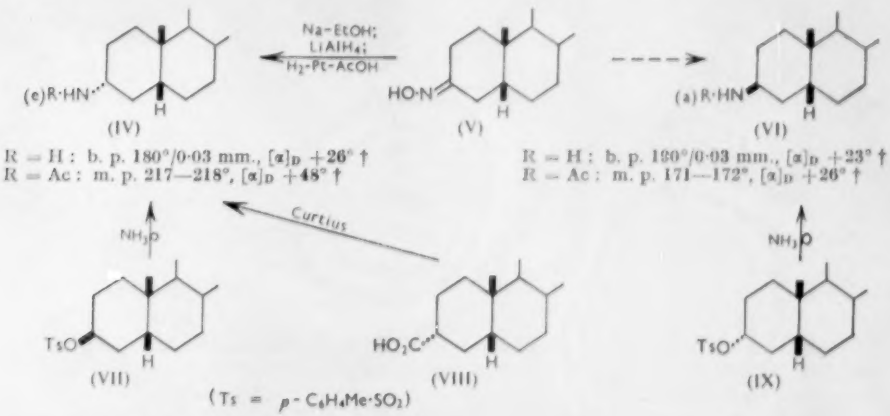
Coprostan-3-one oxime (V) by reduction with sodium in ethanol gave coprostan-3α-ylamine (IV; R = H), identical with the base produced (*a*) by Curtius degradation of coprostane-3α-carboxylic acid[3] (VIII) and (*b*) by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate (VII). Reduction with lithium aluminium hydride gave, contrary to expectation, only coprostan-3α-ylamine (IV; R = H); subsequent reductions with new specimens of the reagent failed, despite extensive variation of the experimental conditions and careful chromatography, to yield coprostan-3β-ylamine (VI; R = H),[8] which was obtained by ammonolysis of coprostan-3α-yl toluene-*p*-sulphonate (IX). Catalytic hydrogenation of coprostan-3-one oxime (V) with platinum in dioxan failed, but in acetic acid proceeded smoothly, rapidly, and contrary to expectation [cf. (II) ⟶ (III)] to give exclusively coprostan-3α-ylamine (IV; R = H), isolated as the acetyl derivative.

The reduction of coprostan-3-one oxime (V) with lithium aluminium hydride to give exclusively coprostan-3α-ylamine [IV; R = H (3α-NH_2 equatorial)] is surprising because under comparable conditions (*a*) pregnan-3-one oxime (as V) yielded mainly pregnan-3β-ylamine [as VI; R = H (3β-NH_2 axial)] as an oil, b. p. 120—140°/0·02 mm., which crystallised, m. p. 65—78°, and was characterised[3] as the acetyl derivative, m. p. 213°, and by

† Values so marked are from this paper.

[4] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[5] McNiven and Read, *J.*, 1952, 153.
[6] Barton, *J.*, 1953, 1027.
[7] Cremlyn, Garmaise, and Shoppee, *J.*, 1953, 1847.
[8] Evans, Shoppee, and Summers, *Chem. and Ind.*, 1954, 1535.
[9] Labler, Czerny, and Sorm, *Chem. Listy*, 1954, **48**, 1058.
[10] Bannard and McKay, *Canad. J. Chem.*, 1955, **33**, 1166.
[11] Dodgson and Haworth, *J.*, 1952, 67.

conversion into the dimethyl derivative, m. p. 124°, identical with a specimen prepared by Professor R. D. Haworth, whilst (*b*) reduction of *allo*pregnan-3-one oxime (as II) with lithium aluminium hydride gave *allo*pregnan-3β-ylamine [as I; R = H (3β-NH_2 equatorial)], identical with the base produced by use of sodium–ethanol.[4] The reduction of pregnan-3-one oxime was repeated at that time to provide more material, with the same result; it should, however, be pointed out that the reduction product was not chromatographed and that some of the epimeric pregnan-3α-ylamine [as IV; R = H (3α-NH_2 equatorial)] may have been formed. We feel convinced however that the principal product was undoubtedly pregnan-3β-ylamine (as VI; R = H), and we can only ascribe the



R = H: b. p. 180°/0·03 mm., $[\alpha]_D$ +26° †
R = Ac: m. p. 217—218°, $[\alpha]_D$ +48° †

R = H: b. p. 190°/0·03 mm., $[\alpha]_D$ +23° †
R = Ac: m. p. 171—172°, $[\alpha]_D$ +26° †

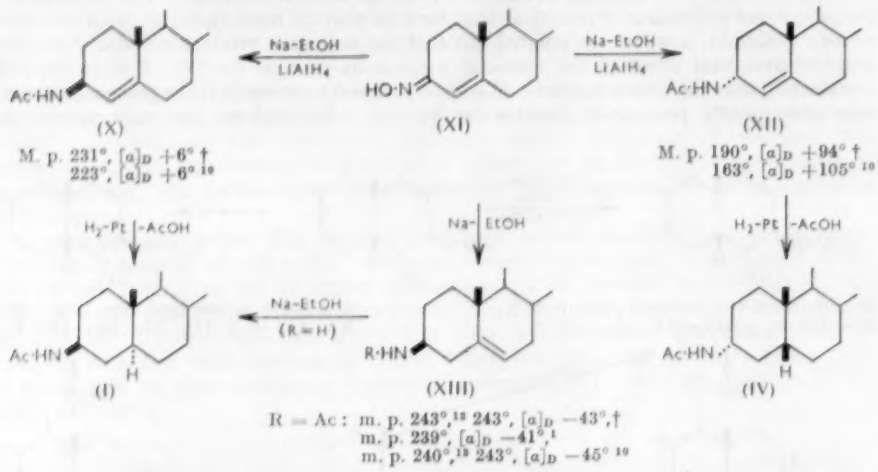
(Ts = *p*-$C_6H_4Me{\cdot}SO_2$)

unexpected difference in behaviour between the coprostane and the pregnane series to long-range effects originating in the side-chain and relayed across a relatively rigid saturated molecule.

The reduction of cholest-4-en-3-one oxime (XI) with sodium in ethanol was first examined by Windaus and Adamla,[12] who by acetylation and fractional crystallisation isolated and identified 3β-acetamidocholest-5-ene (14%), m. p. 243°; further fractional crystallisation and, finally, hand-picking yielded two isomerides, "β-acetylcholesterylamine," m. p. 216—217°, and "γ-acetylcholesterylamine," m. p. 190°. We find that reduction of cholest-4-en-3-one oxime (XI) with sodium in ethanol and chromatography of the acetylated product leads to four compounds. One of these, 3β-acetamidocholest-4-ene (X), appears to correspond with the "β-acetylcholesterylamine" of Windaus and Adamla, and by catalytic hydrogenation with platinum in acetic acid affords 3β-acetamidocholestane (I), whilst another, 3α-acetamidocholest-4-ene (XII), appears to be the "γ-acetylcholesterylamine" of Windaus and Adamla, and by catalytic hydrogenation gives 3α-acetamidocoprostane (IV); the two compounds (X) and (XII) can be more readily prepared by reduction of cholest-4-en-3-one oxime with lithium aluminium hydride. The third compound is 3β-acetamidocholestane (I), which may have arisen by reduction of 3β-acetamidocholest-4-ene (X), or by reduction of the fourth compound 3β-acetamidocholest-5-ene [12,13] (XIII; R = Ac) [as the free base (XIII; R = H) with subsequent acetylation]. The formation of 3β-cholesterylamine (XIII; R = H) in the sodium–ethanol reduction of cholest-4-en-3-one oxime [cf. the sodium–ethanol reduction of cholest-4-en-3-one by Diels and Linn [14]] suggests that in the presence of ethoxide ions an equilibrium is set up between the αβ-unsaturated structure (XIV) and the βγ-unsaturated structure (XVI) in which the former preponderates; addition of a proton to the mesomeric anion (XV)

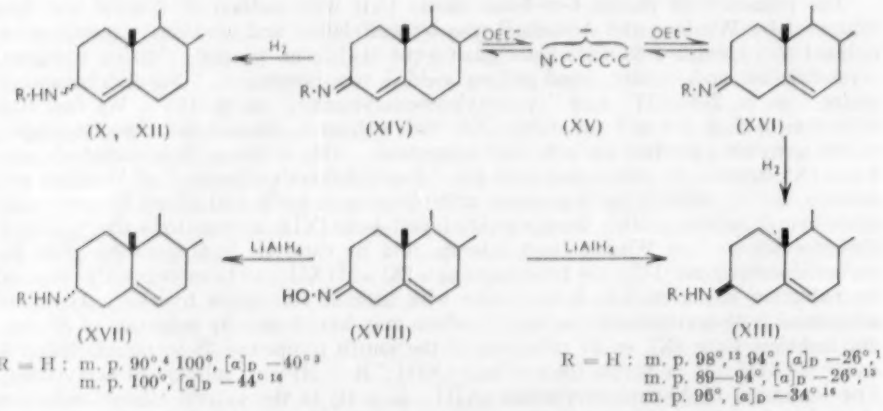
[12] Windaus and Adamla, *Ber.*, 1911, **44**, 3051.
[13] Julian, Magnani, Cole, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.
[14] Diels and Linn, *Ber.*, 1908, **41**, 260; Wagner-Jauregg and Werner, *Z. physiol. Chem.*, 1932, **208**, 72.

under thermodynamic control will lead to production of the epimeric cholest-4-en-3-ylamines (X, XII; R = H), whilst addition to the mesomeric anion (XV) under kinetic control will lead to 3β-cholesterylamine (XIII; R = H).



Reduction of cholest-5-en-3-one oxime [15] (XVIII) with lithium aluminium hydride and chromatographic separation of the resulting bases gave 3β- (XIII; R = H) and 3α-cholesterylamine (XVII; R = H), which were characterised as the acetyl derivatives.

Since this work was completed Bannard and McKay [10] have described the reduction with lithium aluminium hydride of the oximes (XI, XVIII). From cholest-4-en-3-one oxime (XI), they obtained 27% of 3β- (X) and 28% of 3α-acetamidocholest-4-ene (XII) {as a polymorph, m. p. 163°, with substantially the same [α]D (+105°) as our preparation};



from cholest-5-en-3-one oxime (XVIII) by chromatography of the acetylated product they obtained 46% of 3β- (XIII; R = Ac), m. p. 243°, [α]D −45°, and 23% of 3α-acetamidocholest-5-ene (XVII; R = Ac), m. p. 184·5°, [α]D −59°. Bannard and McKay point out that 3α-substituted steroids are generally more dextrorotatory than their 3β-epimerides, and envisage the possibility of reversing the configurations at $C_{(3)}$ of (XIII) and (XVII);

[15] Butenandt and Schmidt-Thomé, *Ber.*, 1936, **69**, 882.
[16] Haworth, Lunts, and McKenna, *J.*, 1955, 986.

this is unnecessary as the correct specific rotation of 3α-acetamidocholest-5-ene is −30°,[3] −31°,[16] and it appears that Bannard and McKay's preparation was contaminated with some difficultly separable and more lævorotatory substance.

Experimental

For general experimental directions, see *J.*, 1956, 1064. $[\alpha]_D$ are in $CHCl_3$.

Cholestan-3α-ylamine and Cholestan-3β-ylamine.—(*a*) Cholestan-3-one oxime (m. p. 192°; 500 mg.) was treated with lithium aluminium hydride (300 mg.) in refluxing ether overnight. The semisolid product (450 mg.) was chromatographed on aluminium oxide (20 g.). Elution with chloroform–methanol (1 : 1) afforded a solid (220 mg.), which by crystallisation from methanol gave plates of cholestan-3α-ylamine, m. p. 87—88°, $[\alpha]_D$ +27° (*c*, 1·1). Elution with methanol gave a solid (200 mg.), which by crystallisation from acetone yielded needles of cholestan-3β-ylamine, m. p. 118—119°, $[\alpha]_D$ +29° (*c*, 0·92).

(*b*) Cholestan-3-one oxime (m. p. 192°; 1·6 g.) was treated with lithium aluminium hydride (1 g.) in refluxing ether for 3 hr. Excess of reagent was destroyed with ethyl acetate at 0°; the precipitated aluminium oxide was filtered off and continuously extracted with ether. After evaporation of the total ethereal extract, the basic products were isolated *via* their hydrochlorides. Acetylation with acetic anhydride in ether at 15° gave a white solid (1·5 g.), which was chromatographed on aluminium oxide (50 g.). Elution with benzene (4 × 100 c.c.) gave a solid (520 mg.), which on recrystallisation from acetone furnished 3α-acetamidocholestane, m. p. 217—218°, $[\alpha]_D$ +36° (*c*, 0·92). Elution with ether–benzene (1 : 9) gave a solid (900 mg.), m. p. 234—245°, which was rechromatographed on aluminium oxide (30 g.), and by elution with benzene (3 × 100 c.c.) also yielded 3α-acetamidocholestane (200 mg.). Further elution with ether–benzene (1 : 9) afforded a solid (650 mg.), which by recrystallisation from acetone gave 3β-acetamidocholestane, m. p. 245—246°, $[\alpha]_D$ +12° (*c*, 1·0).

Cholestan-3α-ylamine.—3α-Acetamidocholestane (200 mg.) was heated under reflux with ethanol (200 c.c.) and concentrated hydrochloric acid (140 c.c.) for 24 hr. The oily product, isolated in the usual way, was chromatographed on aluminium oxide (6 g.); elution with methanol gave cholestan-3α-ylamine as an oil. This was sublimed at 170°/0·03 mm. to afford an oil, which slowly solidified, and, recrystallised from methanol, had m. p. 87—88°, $[\alpha]_D$ +27° (*c*, 1·1).

Cholestan-3β-ylamine.—3β-Acetamidocholestane (200 mg.) was heated under reflux with ethanol (200 c.c.) and concentrated hydrochloric acid (140 c.c.) for 24 hr. The solid product was recrystallised repeatedly from ethanol, to give cholestan-3β-ylamine, m. p. 118°.

Catalytic Reduction of Cholestan-3-one Oxime.—(*a*) Cholestan-3-one oxime (760 mg.) in dioxan (20 c.c.) was shaken under hydrogen in the presence of platinum oxide (140 mg.) for 24 hr. but no reduction of the oxime occurred.

(*b*) Cholestan-3-one oxime (510 mg.) in glacial acetic acid (20 c.c.) was shaken in hydrogen with platinum oxide (100 mg.); the theoretical uptake of hydrogen was attained in 1 hr. The product was acetylated with acetic anhydride in ether at 15°, to yield a solid (500 mg.) which was chromatographed on aluminium oxide (15 g.). Elution with benzene (1 × 50 c.c.) yielded a solid (150 mg.), which by recrystallisation from acetone afforded 3α-acetamidocholestane, m. p. 216—217°. Further elution with benzene gave a solid (330 mg.), m. p. 208°, which was rechromatographed on aluminium oxide (10 g.); elution with benzene again gave 3α-acetamidocholestane (310 mg.), whilst elution with ether–benzene (1 : 9) gave 3β-acetamidocholestane, m. p. 246° (10 mg.), after recrystallisation from ethyl acetate.

Coprostan-3-one Oxime.—Coprostan-3-one was oximated with hydroxylamine acetate in refluxing methanol, and the product (5 g.) chromatographed on aluminium oxide (150 g.). Elution with benzene–pentane (1 : 9) gave coprostan-3-one (120 mg.), whilst elution with acetone afforded the oxime as an oil (4·6 g.). On pouring an ethanolic solution of the oxime into water, a white amorphous solid was obtained, which after intense drying gave coprostan-3-one oxime,[17] m. p. 68°, $[\alpha]_D$ +33° (*c*, 0·92) [Found (after drying at 50°/0·03 mm. for 3 hr.): C, 80·6; H, 11·6. Calc. for $C_{27}H_{47}ON$: C, 80·7; H, 11·8%].

Coprostan-3α-ylamine.—(*a*) Coprostan-3-one oxime (1 g.) in refluxing pentyl alcohol (200 c.c.) was treated with sodium (16 g.) during 3 hr. The solution was worked up in the usual manner and basic material isolated as the pentane-insoluble hydrochloride, which afforded by treatment with ammonia an oily base (900 mg.). The oil was chromatographed on aluminium oxide (10 g.); elution with methanol (10 × 100 c.c.) afforded a yellow oil (800 mg.), which was

[17] Dorée and Gardener, *J.*, 1908, 1625.

distilled at 180°/0·03 mm., to yield *coprostan-3α-ylamine* as a colourless oil, $[\alpha]_D$ +26° (*c*, 1·2) [Found: C, 83·6; H, 12·7. $C_{27}H_{49}N$ requires C, 83·7; H, 12·65%]. Acetylation with acetic anhydride in ether at 15° gave a solid product, which by recrystallisation from acetone furnished *3α-acetamidocoprostane* m. p. 218—219°, $[\alpha]_D$ +48° (*c*, 0·92) [Found (after drying at 100°/0·03 mm. for 3 hr.): C, 80·9; H, 11·9. $C_{29}H_{51}ON$ requires C, 81·1; H, 11·9%].

(*b*) Coprostan-3-one oxime (850 mg.) was treated with lithium aluminium hydride (480 mg.) in refluxing ether for 5 hr. The mixture was worked up in the usual manner to give an oily base (700 mg.) which on acetylation with acetic anhydride in ether at 15° gave a solid which was chromatographed on aluminium oxide (20 g.). Elution with ether–benzene (1 : 9) gave a solid (680 mg.) which by crystallisation from acetone yielded 3α-acetamidocoprostane, m. p. 217—218°.

(*c*) Coprostan-3-one oxime (1 g.) in acetic acid (20 c.c.) was hydrogenated with platinum oxide (325 mg.); the theoretical uptake of hydrogen was attained in 1·5 hr. The oily product was acetylated in ether at 15° to yield a solid (920 mg.), which was chromatographed on aluminium oxide (30 g.). Elution with ether–benzene (1 : 9) afforded only 3α-acetamidocoprostane, m. p. and mixed m. p. 218°.

(*d*) Coprostan-3β-yl toluene-*p*-sulphonate (600 mg.) was heated at 100° in an autoclave with liquid ammonia; the mixture was worked up in the usual manner and acetylated with acetic anhydride in ether at 15° to afford a solid (510 mg.). This was chromatographed on aluminium oxide (15 g.); elution with ether–benzene (1 : 9) gave 3α-acetamidocoprostane, m. p. 217—218°, $[\alpha]_D$ +48° (*c*, 1·0).

Coprostan-3β-ylamine.—Coprostan-3α-yl toluene-*p*-sulphonate (3·9 g.) was heated at 100° in an autoclave with liquid ammonia, the reaction mixture was worked up in the usual manner and the product chromatographed on aluminium oxide (60 g.). Successive elution with benzene, ether, and methanol gave oily fractions, which by distillation at 190°/0·03 mm. gave coprostan-3β-ylamine as an oil, $[\alpha]_D$ +23° (*c*, 0·73) [Found: C, 83·1; H, 12·7. $C_{27}H_{49}N$ requires C, 83·7; H, 12·65%]. Acetylation with acetic anhydride at 100° gave a solid, which by crystallisation from acetone yielded *3β-acetamidocoprostane*, m. p. 172°, $[\alpha]_D$ +26° (*c*, 1·13) [Found (after drying at 100°/0·03 mm.): C, 81·1; H, 12·1. $C_{29}H_{51}ON$ requires C, 81·1; H, 11·9%].

Sodium–Ethanol Reduction of Cholest-4-en-3-one Oxime.—Cholest-4-en-3-one oxime (5 g.), m. p. 153°, in boiling ethanol (200 c.c.) was treated with sodium (20 g.). The product, worked up in the usual way, was an oil, which on acetylation in ether at 15° yielded a solid. This was chromatographed on aluminium oxide (100 g.); elution with benzene–pentane (1 : 1) (4 × 200 c.c.) gave an oil which crystallised from ethyl acetate in needles, m. p. 186—190°, $[\alpha]_D$ +97° (*c*, 1·1). Elution with benzene (3 × 200 c.c.) gave a solid, m. p. 205—222°, and further elution with benzene (8 × 200 c.c.) yielded 3β-acetamidocholest-5-ene, m. p. and mixed m. p. 239—243°, $[\alpha]_D$ −40° (*c*, 0·8). Finally, elution with chloroform–ether gave a small quantity of oil. The fraction, m. p. 205—222° was rechromatographed on aluminium oxide (75 g.); elution with benzene (3 × 100 c.c.) gave oils, but further use of benzene (2 × 100 c.c.) gave a solid, m. p. 182—189°, $[\alpha]_D$ +90°, which crystallised from ethyl acetate in needles, m. p. 189—190°, $[\alpha]_D$ +97° (*c*, 0·73); whilst still further use of benzene (3×100 c.c.) gave a solid, m. p. 228—230°, $[\alpha]_D$ +7° (*c*, 0·7), and final elution with benzene gave mixtures, m. p. 216—235°, and a solid, $[\alpha]_D$ +10° (*c*, 0·85), m. p. 240—244° undepressed on admixture with 3β-acetamidocholestane. The acetylated bases, m. p. 189—190°, $[\alpha]_D$ +97°, and m. p. 228—230°, $[\alpha]_D$ +7°, were identical with 3α- and 3β-acetamidocholest-4-ene respectively described below.

3α-Acetamidocholest-4-ene and 3β-Acetamidocholest-4-ene.—Cholest-4-en-3-one oxime (1·8 g.), m. p. 153°, in ether (200 c.c.) was refluxed with lithium aluminium hydride (1·6 g.) for 4 hr. Working up the product in the usual way, followed by acetylation in ether at 15°, gave a yellow solid (1·8 g.), which was chromatographed on aluminium oxide (60 g.). Elution with benzene–pentane (1 : 1) gave a small amount of oil, which by crystallisation from ethyl acetate gave *3α-acetamidocholest-4-ene*, m. p. 190°, $[\alpha]_D$ +94° (*c*, 1·23) [Found (after drying at 25°/0·03 mm. for 16 hr.): C, 81·7; H, 11·4. $C_{29}H_{49}ON$ requires C, 81·5; H, 11·5%]. Further elution with benzene–pentane (1 : 1) and ether–benzene gave a solid (1 g.), which by crystallisation from ethyl acetate gave *3β-acetamidocholest-4-ene*, m. p. 231°, $[\alpha]_D$ +6° (*c*, 0·87) [Found (after drying at 25°/0·03 mm. for 16 hr.): C, 81·3; H, 11·3%].

3α-Acetamidocoprostane.—3α-Acetamidocholest-4-ene (20 mg.) in glacial acetic acid (10 c.c.) was hydrogenated with platinum oxide (10 mg.) for 2 hr. Working up in the usual way gave a solid, which crystallised from acetone in plates, m. p. 180—215°, and after sublimation (210°/0·01 mm.) and recrystallisation from ethyl acetate gave 3α-acetamidocoprostane, m. p. 215°, mixed m. p. 212—215°, $[\alpha]_D$ +47° (*c*, 0·8).

3β-*Acetamidocholestane*.—3β-Acetamidocholest-4-ene (350 mg.) in glacial acetic acid (20 c.c.) and ether (100 c.c.) was hydrogenated with platinum oxide (100 mg.) for 4 hr. Working up in the usual way gave a solid (350 mg.), which was chromatographed on aluminium oxide (10 g.). Elution with benzene gave a solid, which crystallised from acetone in plates, $[\alpha]_D$ +12° (*c*, 1·12), m. p. 241—243°, undepressed on admixture with 3β-acetamidocholestane.

[With J. H. Pierce] *Cholest-5-en-3β-ylamine and Cholest-5-en-3α-ylamine*.—Cholest-5-en-3-one oxime (9 g.), m. p. 188°, in boiling ether (200 c.c.) was reduced with lithium aluminium hydride (5 g.). The mixture of bases was isolated as an oil (7·9 g.), and a portion (6 g.) was chromatographed on aluminium oxide (180 g.). Elution with benzene–pentane and with benzene gave uncrystallisable oils, whilst ether–benzene (1 : 9) (20 × 100 c.c.) gave an oil, which crystallised (m. p. 86—88°) and after distillation at 130°/0·02 mm. yielded cholest-5-en-3α-ylamine as needles (from cooled pentane), m. p. 100°, $[\alpha]_D$ −40° (*c*, 0·89). Acetylation in ether at 15° yielded 3α-acetamidocholest-5-ene, which crystallised from acetone as needles, m. p. 186—189°, $[\alpha]_D$ −30° (*c*, 1·0). Elution with ether–benzene (1 : 4) gave oils, whilst ether (18 × 100 c.c.) gave an oil, which on crystallisation from acetone yielded needles, m. p. 138—140° undepressed by the *iso*propylidene derivative of cholest-5-en-3β-ylamine. Acetylation gave 3β-acetamidocholest-5-ene, m. p. and mixed m. p. 243°.

[With J. H. Pierce] allo*Pregnan*-3β-*ylamine*.—*allo*Pregnan-3-one oxime (m. p. 196°; 0·5 g.) in boiling ethanol (20 c.c.) was reduced with sodium (4 g.). Working up in the usual way gave an oil, which by distillation at 130—140°/0·01 mm. gave allo*pregnan*-3β-*ylamine*, m. p. 119°, $[\alpha]_D$ +6·6° (*c*, 1·2) (Found: C, 82·9; H, 12·1. $C_{21}H_{37}N$ requires C, 83·3; H, 12·0%). Acetylation with acetic anhydride in ether at 15° gave a solid, which after sublimation at 220—240°/0·01 mm. and crystallisation from acetone gave 3β-*acetamido*allo*pregnane*, m. p. 266—268°, $[\alpha]_D$ 0° (*c*, 0·5) [Found (after drying at 100°/0·01 mm. for 4 hr.): C, 79·8; H, 11·4. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·4%].

*allo*Pregnan-3-one oxime (250 mg.) was treated with lithium aluminium hydride (150 mg.) in refluxing ether for 5 hr. Working up in the usual way gave an oil, which by acetylation with acetic anhydride in ether at 15° and crystallisation from ethyl acetate gave needles, m. p. 265°, undepressed by the above specimen of 3β-acetamido*allo*pregnane.

One of us (D. H. E.) acknowledges the financial support of Monsanto Chemicals Ltd., and another (H. C. R.), the award of a University Postgraduate Studentship; we thank Glaxo Laboratories Ltd. for gifts of cholesterol and for performing the ammonolysis recorded above.

University of Wales, University College, Swansea. [*Received, October 31st*, 1955.]

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328. *Chlorophyll and Related Substances. Part III.* The Synthesis of Octamethylchlorin.*

By Ulli Eisner and R. P. Linstead, with (in part) E. A. Parkes and Edith Stephen.

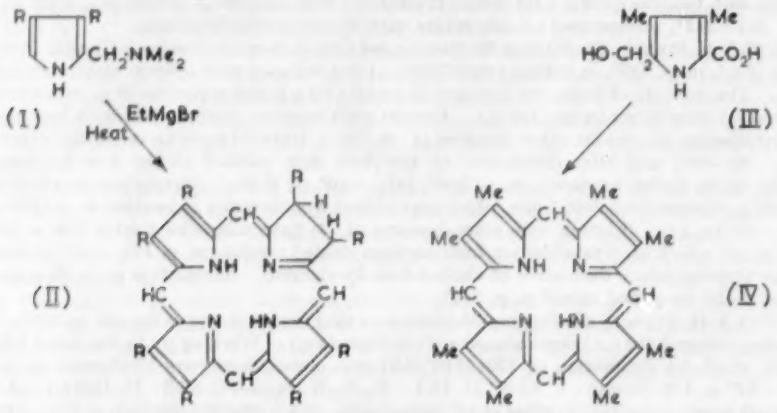
Octamethylchlorin (II; R = Me) and octamethylporphin (IV) have been synthesised from 2-dimethylaminomethyl-3 : 4-dimethylpyrrole (I; R = Me) in good yield. Metal derivatives of both pigments have been prepared and light-absorption data are given. The quantitative dehydrogenation of octamethylchlorin and of its magnesium derivative has been studied.

In Part I* the synthesis of chlorin (II; R = H) from 2-dimethylaminomethylpyrrole (I; R = H) was described. It was of interest to determine whether the new method, which is unique in providing the first direct synthesis of a dihydroporphyrin derivative, was general and could be applied to the synthesis of substituted chlorins. It was also desirable to study a substituted chlorin, closer in structure to those derived from chlorophyll, particularly from the viewpoint of its quantitative dehydrogenation.

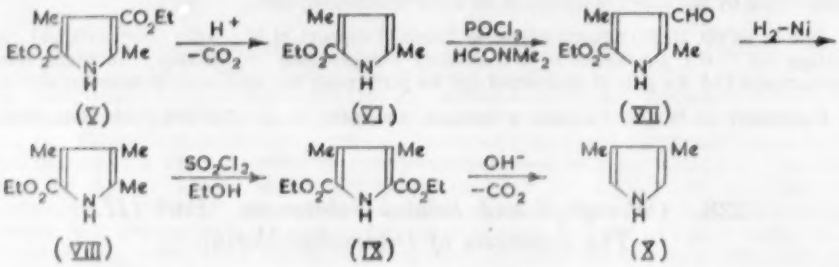
It was decided to prepare a symmetrically substituted pigment in order to avoid the formation of a mixture of positional isomers. Our choice fell on the unknown octamethylchlorin (II; R = Me). The corresponding porphin (IV) has been prepared in up to 25%

* Parts I and II, *J.*, 1955, 3742, 3749.

yield by Fischer and Walach,[1] and more recently by Siedel and Winkler [2] who employed 5-hydroxymethyl-3 : 4-dimethylpyrrole-2-carboxylic acid (III) as intermediate.



The synthesis of the unknown 2-dimethylaminomethyl-3 : 4-dimethylpyrrole (I; R = Me) was accordingly undertaken. This involved the large-scale preparation of 3 : 4-dimethylpyrrole (X) which had previously been prepared in small amounts.[3,4,5] We employed the following series of reactions, which are essentially those used by earlier workers :



This synthesis was carried out by Dr. E. A. Parkes, who showed that excellent yields could be obtained in all stages up to and including the preparation of the pyrrolic ester (VIII). The modifications by Chu and Chu [6] were used in the preparation of the pyrroles (VI) and (VII); the ester (VIII) was prepared by catalytic reduction of the ester (VII).[5] Difficulties, however, were encountered in the preparation of the diester (IX). Fischer and Höfelmann's method [5] was tried without success as was the modification by Corwin [7] *et al.* The desired product (IX) was finally obtained in 76% yield by strict control of the reaction conditions, in particular by working at a low temperature. The hydrolysis and decarboxylation of the diester (IX) were carried out by modifications of the methods of Fischer and Höfelmann [5] or of Chu and Chu,[6] whereby 3 : 4-dimethylpyrrole (X) was obtained in 50% yield.

[1] Fischer and Walach, *Annalen*, 1926, **450**, 164.
[2] Siedel and Winkler, *ibid.*, 1943, **554**, 162.
[3] Fischer and Walach, *ibid.*, 1926, **450**, 109.
[4] Fischer and Hiernels, *ibid.*, 1932, **492**, 32.
[5] Fischer and Höfelmann, *ibid.*, 1938, **533**, 216.
[6] Chu and Chu, *J. Org. Chem.*, 1954, **19**, 266.
[7] Corwin, Bailey, and Viohl, *J. Amer. Chem. Soc.*, 1942, **64**, 1267; Corwin and Straughn, *ibid.*, 1948, **70**, 1416.

Treatment of the pyrrole (X) with dimethylamine and formaldehyde [8] afforded the crystalline Mannich base (I; R = Me) in 90% yield.

The reaction of the base (I; R = Me) with 1 mol. of ethylmagnesium bromide in boiling xylene or *o*-dichlorobenzene afforded a mixture of the magnesium complexes of octamethylporphin (IV) and -chlorin (II; R = Me). The yields of the chlorin were of the order of 5—12·5%, and those of the porphin 20—36%. It was subsequently found that octamethylchlorin (II; R = Me) is much more readily dehydrogenated than chlorin (II; R = H) itself and the preponderance of octamethylporphin (IV) in the reaction mixture is therefore not surprising. The total yields of macrocyclic pigment obtained are quite good for a method involving a monopyrrolic intermediate; they could probably be improved by suitable variations of the reaction conditions.

A rough preliminary separation was achieved by filtration of the crude insoluble magnesium octamethylporphin. The magnesium octamethylchlorin which remained in the filtrate was converted into the metal-free pigment by treatment with cold dilute hydrochloric acid. In contrast to unsubstituted chlorin (II; R = H) [9] octamethylchlorin was readily purified by adsorption chromatography on alumina. This treatment separated from it traces of the porphin (IV), as well as a green pigment with spectral characteristics very similar to those of octamethylchlorin. The green pigment has not yet been obtained pure, but it may well be analogous to the " oxychlorin " obtained in the earlier work.[9] In support of this idea it should be pointed out that its light absorption is similar to that of a pigment obtained by Fischer *et al.*[10] from the oxidation of octamethylporphin with hydrogen peroxide–sulphuric acid, a reaction which is known to produce "oxychlorins."

Octamethylchlorin is a deep blue crystalline solid. The solutions in benzene are green with an intense red fluorescence.

The light absorption of octamethylchlorin has been measured in benzene over the range 350—700 mμ. The results are given in detail in the Table and the Figure. The spectrum bears a close resemblance to both that of chlorin [9] and of ætiochlorin.[11]

When a benzene solution of octamethylchlorin was heated with methanolic cupric acetate, copper octamethylchlorin separated from the blue solution as purple crystals. It was purified by chromatography on heavy magnesium oxide to remove a trace of copper octamethylporphin, but was not obtained quite pure even after this treatment. Light-absorption data are given in the Table.

A solution of magnesium octamethylchlorin was prepared by treatment of a benzene solution of the chlorin (II; R = Me) with ethylmagnesium bromide. The solution was blue with an intense red fluorescence. Light-absorption data are given in the Table. The metal is extremely labile in this compound, being partially removed even by cold aqueous ammonium chloride or by traces of hydrogen chloride (see below). In this it differs markedly from unsubstituted magnesium chlorin.

The second product, magnesium octamethylporphin (XI), was purified by repeated extraction with boiling benzene. It was, however, still contaminated with magnesium octamethylchlorin which was dehydrogenated to the porphin (XI) by extraction into benzene containing an excess of 1 : 4-benzoquinone. Two such treatments afforded magnesium octamethylporphin (XI) containing only traces of the chlorin derivative. The magnesium complex (XI) forms purple microcrystals. Its solutions are rose-red with a red fluorescence. Its spectrum (Table) shows a considerable solvent effect. By treatment with cold dilute hydrochloric acid, the porphin (XI) is converted into octamethylporphin (IV), spectroscopically identical with a specimen prepared by standard methods.[2]

When the magnesium porphin (XI) was treated with boiling acetic acid and cupric acetate, copper octamethylporphin was formed as purple microcrystals. Light-absorption data (Table) are in agreement with values recorded by Fischer and Walach [1] and are very similar to those of copper ætioporphyrin II.[12] It is remarkable that, in spite of its

[8] Herz and Rogers, *J. Amer. Chem. Soc.*, 1951, **73**, 4921.
[9] Eisner and Linstead, *J.*, 1955, 3742.
[10] Fischer, Halbig, and Walach, *Annalen*, 1927, **452**, 268.
[11] Pruckner, *Z. phys. Chem.*, 1940, **187**, *A*, 257.
[12] Erdman and Corwin, *J. Amer. Chem. Soc.*, 1946, **68**, 1885.

preparation in acid medium, traces of the octamethylchlorin derivative, originally present in (XI), persist in copper octamethylporphin. The apparent stability of the copper complex of octamethylchlorin is not paralleled by the behaviour of the corresponding derivatives in the unsubstituted series.[9]

Light-absorption data.

Octamethylchlorin in benzene [a]

$\lambda_{max.}$ mμ	390 †	488	496	522	548	594	618	646
ε	175,000	12,900	13,100	4,300	1,800	4,500	4,600	58,500

Ætiochlorin in dioxan [b]

$\lambda_{max.}$ mμ	488	494	519	522	542	564	586	613	642
ε	13,200	13,400	4,200	4,100	1,800	1,200	4,000	4,100	59,400

Magnesium octamethylchlorin in benzene [a]

$\lambda_{max.}$ mμ	405·5 †	512·5	549	578	621
ε	231,000	7,600	5,000	10,500	70,400

Copper octamethylchlorin in benzene [a]

$\lambda_{max.}$ mμ	399·5	494	532	573	615
ε	147,000	5,400	5,100	8,200	44,100

Octamethylporphin in o-dichlorobenzene [a]

$\lambda_{max.}$ mμ	402 †	499	533	570	594 *	624
ε	146,000	13,100	9,300	6,400	1,700	5,100

Ætioporphyrin II in dioxan [c]

$\lambda_{max.}$ mμ	496	528	566	595	621
ε	14,000	10,000	6,600	1,300	5,800

Magnesium octamethylporphin in benzene—8% pyridine [a]

$\lambda_{max.}$ mμ	411·5 †	422 †	499	547	582
ε	264,000	118,000	3,900	14,000	10,600

Magnesium octamethylporphin in pyridine [a]

$\lambda_{max.}$ mμ	412 †	423 †	507 *	555	582
ε	180,000	228,000	2,800	16,100	7,900

Copper octamethylporphin in chlorobenzene [a]

$\lambda_{max.}$ mμ	399 †	527	563
ε	318,000	13,400	27,700

Copper ætioporphyrin II in dioxan [d]

$\lambda_{max.}$ mμ	398 †	527	563
ε	225,000	14,000	24,200

* Inflection † Soret band.

References : *a*, This work. *b*, Pruckner, ref. 11. *c*, Stern and Wenderlein, *Z. phys. Chem.*, 1934, **170**, *A*, 337. *d*, Erdman and Corwin, ref. 12.

Octamethylchlorin is readily dehydrogenated to the porphin (IV) by quinones. Thus the reaction with excess of 2 : 3-dichloro-5 : 6-dicyano-1 : 4-benzoquinone is instantaneous in the cold, and with tetrachloro-1 : 2-benzoquinone it is complete after 5 min. at 80°. Quantitative dehydrogenations with dichlorodicyano-1 : 4-benzoquinone, carried out by Miss Stephen, show that octamethylchlorin is completely dehydrogenated by 1 mol. of quinone and that the relationship, % dehydrogenation : mols. of quinone, is linear. This is in agreement with the dihydro-structure assigned to octamethylchlorin.

Magnesium octamethylchlorin was slowly dehydrogenated to (XI) in the cold by tetrachloro-1 : 2-benzoquinone. Quantitative results could, however, not be obtained because partial demetallation occurred, presumably by traces of hydrogen chloride produced in the

reaction or by the action of the acidic tetrachloroquinol. The reaction with dichlorodicyano-1 : 4-benzoquinone was instantaneous. As in the case of metal-free octamethylchlorin, the results confirm the dihydro-level of the magnesium derivative.

The structure of octamethylchlorin (II; R = Me) is therefore established and the synthesis of chlorins from a Mannich base such as (I) thus appears to be applicable to β-substituted chlorins.

Experimental

(Microanalyses by Mr. Oliver of this Department.)

3 : 4-*Dimethylpyrrole*. (With Dr. E. A. Parkes.)—The pyrrole derivatives (V)—(VIII) were prepared by standard methods.

Diethyl 3 : 4-*dimethylpyrrole*-2 : 5-*dicarboxylate* (IX). Freshly distilled sulphuryl chloride (47 g., 3 mols.) was added dropwise with vigorous stirring during 2·5—3 hr. to ethyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate (VIII) suspended in anhydrous ether (150 c.c.) at −15° to −20°. The precipitate redissolved when the addition of sulphuryl chloride was almost complete. After being kept at 0° overnight the unchanged reagent was decomposed by the dropwise addition of water (10 c.c.) at <20°. The ethereal solution was dried (Na_2SO_4), the solvent removed under reduced pressure, and the oily residue treated dropwise with ethanol (80 c.c.) at room temperature with external cooling. The solution was heated to boiling for 5 min., the excess of ethanol removed under reduced pressure, and the residue dissolved in ether (200 c.c.). The ethereal solution was washed successively with aqueous sodium hydroxide, sodium hydrogen sulphite solution, and water, and dried (Na_2SO_4), and the volume reduced to 80 c.c. under reduced pressure. On rapid cooling the solution deposited crystals of the diester (IX) (16·2 g.), m. p. 67—68° (lit., m. p. 73°). A second crop (5·3 g.) was obtained by distillation of the mother liquors at 100°/10^{-3} mm. This distillate after one crystallisation from 80% ethanol, had m. p. 69—70° (3·8 g.). The total yield was 20 g. (76%) of material sufficiently pure for the next stage.

3 : 4-*Dimethylpyrrole* (X). (*a*) The diester (IX) (13·1 g.) was boiled under reflux with a solution of sodium hydroxide (15 g.) in water (30 c.c.) in an atmosphere of nitrogen. Excess of water was distilled off and the residue was heated to 250—350° under reduced pressure for 4 hr. The aqueous distillate was saturated with sodium chloride, and extracted with ether (5 times) in an atmosphere of nitrogen. The solid residue was dissolved in the minimum quantity of water and extracted with ether. The combined ethereal extracts were dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue distilled, affording 3 : 4-dimethylpyrrole (2·6 g., 50%) as low-melting crystals, b. p. 88—90°/22—24 mm. (lit., b. p. 65—66°/14 mm., m. p. 33°).

(*b*) The diester (14·9 g.) in 10% sodium hydroxide solution (60 c.c.) was boiled under reflux for 1 hr. The solution was cooled to 0° and acidified, and the precipitate was filtered off, dried, and boiled under reflux with 2-aminoethanol (10 c.c.) for 1 hr. The solution was cooled, neutralised with acetic acid, and repeatedly extracted with ether. The ethereal extracts were washed with aqueous copper sulphate followed by sodium hydrogen carbonate solution and dried (K_2CO_3). Removal of the solvent and distillation under reduced pressure afforded 3 : 4-dimethylpyrrole (2·65 g., 45%).

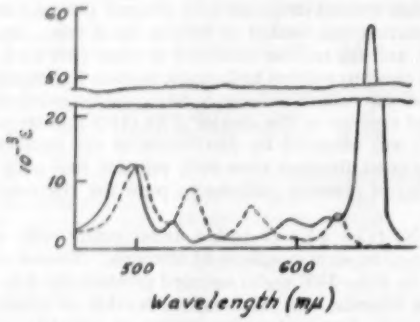
2-*Dimethylaminomethyl*-3 : 4-*dimethylpyrrole* (I; R = Me).—3 : 4-Dimethylpyrrole (X) (2·65 g., 1 mol.) in methanol (10 c.c.) was treated with a solution of dry dimethylammonium chloride (2·36 g., 1·05 mol.), potassium acetate (2·9 g., 1 mol.), and 40% aqueous formaldehyde solution (2·3 g.) in water (10 c.c.) at −5° to 5° in an inert atmosphere. The solution was kept at 0° for 2 hr., acidified, and extracted with ether. The aqueous layer was basified (NaOH) and extracted with ether. The ethereal extracts were washed with water, and dried ($MgSO_4$) for 1 hr., and the solvent removed under reduced pressure. Distillation of the residue in a high vacuum afforded the pure *Mannich base* (3·78 g., 89%) as a crystalline solid, m. p. 46—47°, b. p. 55°/0·2 mm. (Found: C, 70·8; H, 10·6; N, 18·4. $C_9H_{16}N_2$ requires C, 71·0; H, 10·6; N, 18·4%). The *picrate*, prepared from the base (56 mg.) and picric acid (85·5 mg.) in methanol, was obtained as bright yellow crystals, m. p. 110—112° (Found: C, 47·1; H, 5·1; N, 18·6. $C_9H_{16}N_2,C_6H_3O_7N_3$ requires C, 47·2; H, 5·0; N, 18·4%). It darkened on attempted crystallisation.

Preparation of Octamethylchlorin (II; R = Me).—The Mannich base (I; R = Me) (696 mg.) in xylene (50 c.c.) was treated with ethylmagnesium bromide (1 mol.) in ether (1·3 c.c.). The

solution was boiled under reflux in an atmosphere of oxygen-free nitrogen for 10 hr., cooled, and filtered, and the residue washed with cold benzene. The combined filtrate and washings were shaken with 2N-hydrochloric acid and basified with ammonia solution. The benzene solution was concentrated to 250 c.c. under reduced pressure and the intensity of the main band at 646 mμ was determined spectroscopically after an appropriate dilution. From spectral data subsequently determined for pure octamethylchlorin, the concentration of the crude product was calculated to be 12·5% (60·7 mg.). The residual solid (see above) was continuously extracted with boiling benzene in an atmosphere of nitrogen, affording magnesium octamethylporphin (XI) (see below). The mother liquors contained more magnesium octamethylchlorin which was converted into the metal-free pigment.

With a reaction period of 20 hr., the yield of octamethylchlorin was 6·6% and that of magnesium octamethylporphin was 36·5%. In boiling *o*-dichlorobenzene (6 hr.) the yields were 5·2% and 22%, respectively.

Purification of Octamethylchlorin.—The crude benzene extracts from the above preparations were evaporated under reduced pressure and chromatographed on alumina (grade I), benzene–ether (9 : 1) being used as eluant. Octamethylchlorin was eluted first as a green diffuse band. Gradual increase of the ether concentration eluted octamethylporphin as a pink band, followed by a narrow dark green band of " octamethyloxychlorin " which was eluted with ether. The



Absorption spectra :
—— *Octamethylchlorin (in benzene).*
- - - - *Octamethylporphin (in o-dichlorobenzene).*

latter pigment, which was not obtained pure, had light-absorption maxima at 389·5, 495, 530, 586, and 641 mμ; $E^{1\%}_{1cm.}$ = 2375, 211·5, 11·0, 8·65, 438·4.

The octamethylchlorin was rechromatographed on alumina with benzene–ether (19 : 1) as eluant. Concentration of the solution under reduced pressure in an atmosphere of nitrogen afforded deep blue crystals of *octamethylchlorin* which after one crystallisation from benzene were analytically pure (Found : C, 79·5, 79·45; H, 7·9, 7·8; N, 13·4%; C/H, 10·1, 10·2. $C_{36}H_{32}N_4$ requires C, 79·2; H, 7·6; N, 13·2%; C/H, 10·4).

Copper Octamethylchlorin.—Octamethylchlorin (14 mg.) in boiling benzene was treated with a slight excess of cupric acetate in methanol in an atmosphere of nitrogen. The solution was cooled, diluted with benzene, and washed with aqueous ammonia and water. The solution was concentrated and chromatographed on heavy magnesium oxide. Elution was carried out with benzene containing 20—30% ether until a separation was achieved between the faster-moving blue band of copper octamethylchlorin and the pink band of the corresponding porphin derivative. The column was then extruded and the two zones separated mechanically. Elution with chloroform, evaporation of the solution under reduced pressure, and addition of methanol afforded *copper octamethylchlorin* as deep blue crystals (Found : Cu, 13·7. $C_{36}H_{30}N_4Cu$ requires Cu, 13·1%).

Magnesium Octamethylchlorin.—A solution of octamethylchlorin in benzene was treated with excess of ethereal ethylmagnesium bromide, water was added at 10—20°, and the solution was filtered from magnesium hydroxide. All operations were carried out in an atmosphere of nitrogen in diffuse light. The blue benzene solution was made up to 50 c.c. and the light absorption determined immediately (see Table). Aliquot portions were treated with 2N-hydrochloric acid to convert it into the metal-free pigment, the concentration of which was determined spectroscopically.

Octamethylporphin (IV).—The crude pigment was prepared in 28% yield by Siedel's method.[3] After three continuous extractions from a thimble by boiling *o*-dichlorobenzene, it was obtained

analytically pure as purple microcrystals (Found : C, 79·6; H, 7·3; N, 13·3%; C/H, 10·9. Calc. for $C_{28}H_{30}N_4$: C, 79·6; H, 7·2; N, 13·3%; C/H, 11·1). For light-absorption data, see the Table and the Figure. It could not be converted into the magnesium derivative on account of its insolubility.

Magnesium Octamethylporphin (XI).—The crude pigment (629 mg.) (see above) was placed in a thimble and continuously extracted into a solution of benzene containing 1 : 4-benzoquinone (160 mg.). Treatment was repeated and the pigment was finally extracted into pure benzene. *Magnesium octamethylporphin* separated as purple microcrystals (Found : C, 75·3; H, 6·5; N, 12·8; Mg, 5·75. $C_{28}H_{28}N_4Mg$ requires C, 75·6; H, 6·3; N, 12·6; Mg, 5·5%). It was converted into octamethylporphin by treatment of a benzene solution with cold 2N-hydrochloric acid. The precipitated hydrochloride was suspended in ammonia solution and filtered. The spectrum of the pigment (in *o*-dichlorobenzene) was identical with that of the material prepared by Siedel's method.

Copper Octamethylporphin.—Magnesium octamethylporphin (40 mg.) was placed in a thimble and continuously extracted into a solution of cupric acetate in acetic acid. The precipitated *copper octamethylporphin* was crystallised twice from pyridine (Found : C, 69·8, 69·9; H, 6·2; 6·1; N, 12·1. $C_{28}H_{28}N_4Cu$ requires C, 69·5; H, 5·8; N, 11·6%).

Dehydrogenation Experiments (With Edith Stephen).—(a) *Octamethylchlorin.* The techniques used were essentially those described in Part II.[13] A solution of octamethylchlorin (0·0236 g./l.; $5·5 \times 10^{-6}$M) in purified *o*-dichlorobenzene was treated with dichlorodicyano-1 : 4-benzoquinone. The mixed solutions were either sealed into ampoules (in the case of a long reaction period) or mixed in volumetric flasks. All experiments were carried out in the dark at room temperature. The concentration of pigments was determined spectroscopically from the absorption band at 645 mμ for octamethylchlorin and at 535 and 570 mμ for octamethylporphin. The intensities of the last two bands being relatively low, results calculated from them do not have the same accuracy as those calculated from the 645 mμ band. For 1 mol. of octamethylchlorin, the following results were obtained :

Mols. quinone	Time, hr.	Unchanged chlorin, %	Porphin formed, % (535 mμ)	(570 mμ)
1	18	2	100	102
1	18	4	98	106
0·84	0·5	15	88	90
0·6	0·5	33	65	67
0·5	0·5	47	49	53
0·42	0·5	58	40	45
0·33	0·5	69	29	30
0·25	0·5	76	18	17

(b) *Magnesium octamethylchlorin.* The dehydrogenations were carried out at room temperature in benzene solution with dichlorodicyanoquinone. Spectrophotometric measurements (of bands at 620, 545, and 580 mμ) were made immediately after mixing the solutions :

Mols. quinone	Unchanged chlorin, %	Porphin formed, % (545 mμ)	(580 mμ
1	13	86	89
1	7	87	92
1	5	93	100
1	0	95	99
0·5	49	42	42
0·5	50	47	46
0·5	50	43	42

The work has been made possible by financial support from the Rockefeller Foundation, whom we thank. Dr. Parkes carried out his part in this work during the tenure of a Shell Fellowship, and Miss Stephen during the tenure of a Union Post Graduate Scholarship.

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London, S.W.7.

[*Received, November 1st*, 1955.]

[13] Eisner and Linstead, *J.*, 1955, 3749.

329. *The β-Phenylserine Series. Part IV.**

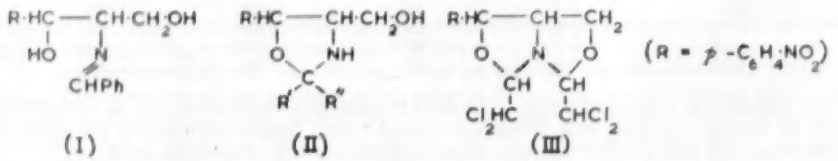
By Ernst D. Bergmann and H. Resnick.

Condensation of the diastereoisomeric 2-amino-1-*p*-nitrophenylpropane-1 : 3-diols, of *threo*- and *erythro*-phenylserine ethyl ester, and of (±)-ephedrine with aldehydes and ketones has been studied. The structures of the products (oxazolidines or Schiff's bases) have been determined with the aid of the infrared spectra. No difference has been observed in the behaviour of the diastereoisomerides; the reactions are not accompanied by change in configuration.

From the two 2-amino-1-*p*-nitrophenylpropane-1 : 3-diols and an excess of dichloroacetaldehyde, diastereoisomeric 3 : 7-dioxa-1-aza-*bicyclo*[3 : 3 : 0]-octane derivatives (III) were formed by double condensation.

The α-amino-alcohol grouping in β-phenylserine, in chloramphenicol, and in related compounds appeared likely to condense with carbonyl compounds. As α-amino-alcohols with aldehydes and ketones give either oxazolidines of Schiff's bases, depending on the structure of the reactants,[1] it appeared of interest to study whether the configuration or conformation of the above-named substances influences the course of the reaction or its rate. According to Fodor and his co-workers,[2] the 1-hydroxy- and the 2-amino-group in *threo*-chloramphenicol are near to each other, in the *erythro*-isomer in a *trans*-like position. Thus, ephedrine and *ψ*-ephedrine react differently with urea[4] and their *N*-carbamoyl derivatives cyclise differently; and the *N*-thiobenzoyl derivatives of *threo*-amino-alcohols cyclise to Δ^2-thiazolines, whilst in the *erythro*-series Δ^2-oxazolines are formed.[5] However, the expectation has not been fulfilled.

2-Amino-1-*p*-nitrophenylpropane-1 : 3-diol was condensed with dichloroacetaldehyde, diethyl ketone, *cyclo*hexanone, and benzaldehyde by azeotropic distillation. With benzaldehyde, only the *threo*-, but not the *erythro*-derivative, gave a crystalline product. As in other similar cases,[1] the *threo*-product proved to be the Schiff's base (I) (infrared band

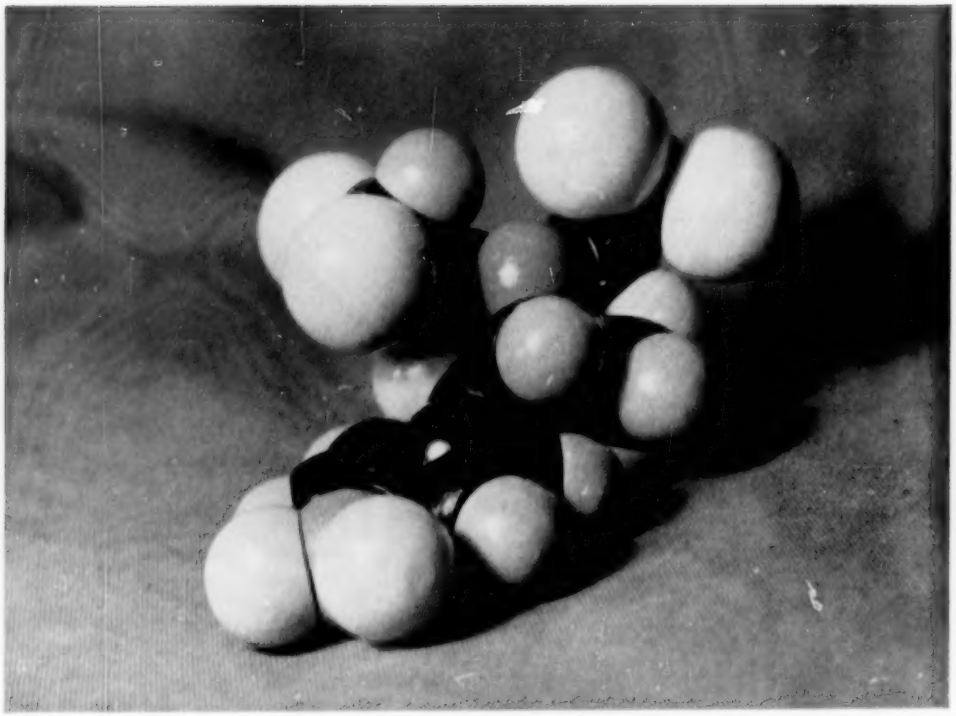


at 1670 cm.$^{-1}$ due to the azomethine system). In the other cases studied, the products had a cyclic structure (II) showing in the 1080—1200 cm.$^{-1}$ region bands characteristic of the oxazolidine ring.[6] The ultraviolet spectra of the compounds of both series show two bands (2320—2345 Å; 2700—2750 Å) which correspond to those of nitrobenzene.[7] The assumption that the secondary, and not the primary, hydroxy-group participates in the formation, is based on the strong infrared band in the region characteristic of a primary hydroxyl group (1030—1060 cm.$^{-1}$). It appears that the phenyl group activates the neighbouring hydroxyl group as in benzyl alcohol.

The products of the *threo*- and the *erythro*-series were different and homogeneous. In their formation, a small but significant difference in rate was observed. For complete

* Part III, *J.*, 1954, 1064.

[1] Bergmann, *Chem. Rev.*, 1953, **53**, 309.
[2] Fodor *et al.*, (*a*) *J.*, 1951, 1858; (*b*) *J.*, 1952, 850; (*c*) *J. Org. Chem.*, 1949, **14**, 337.
[3] Cf. Kanzawa, *Pharm. Bull. (Japan)*, 1955, **3**, 71.
[4] Close, *J. Org. Chem.*, 1950, **15**, 1131.
[5] Sicher, 14th Internat. Congr. Pure Appl. Chem., Zürich, 1955.
[6] Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 168.
[7] Wolf and Herold, *Z. phys. Chem.*, 1931, **13**, *B*, 201.



[To face p. 1005

reaction (which was measured by the quantity of water liberated azeotropically) the following times (in minutes) were required :

	$CHCl_2$·CHO	$COEt_2$	*cyclo*Hexanone
threo	120	110	175
erythro	180	170	190

Whilst diethyl ketone and *cyclo*hexanone gave the oxazolidines (II) even when employed in excess, an excess of dichloroacetaldehyde led to the formation of a *threo*- and an *erythro*-3 : 7-dioxa-1-aza*bicyclo*[3 : 3 : 0]octane derivative (III). The infrared spectrum proves the absence of the C=N system and the presence of oxazolidine rings. A model shows (Plate) that for steric reasons only aldehydes will be able to give a system such as (III); even two methylene or methyl groups in the immediate vicinity of the carbonyl group would cause too great a deformation of the molecular structure. After this paper had been completed, Pedvazzoli [8] reported similar observations.

threo- and *erythro*-Phenylserine ethyl ester were condensed with benzaldehyde, *p*-nitrobenzaldehyde, *p*-anisaldehyde, 2 : 4-dichlorobenzaldehyde, butyraldehyde, *cyclo*pentanone, *cyclo*hexanone, and *cyclo*heptanone. The reactions went easily to completion, but mostly gave resins; only from *cyclo*hexanone were two crystalline derivatives obtained; benzaldehyde gave a well-defined compound with the *threo*-ester. These three products were Schiff's bases, showing the C=N frequency at 1678, 1670, 1665 $cm.^{-1}$, respectively, and the hydroxyl frequency at 3380, 3310, and 3450 $cm.^{-1}$. The location of the hydroxyl bands makes it probable that the products contain hydrogen bonds involving the ester carbonyl group.

For comparison, the behaviour of (±)-ephedrine (*erythro*) towards aldehydes and ketones was studied: in this case, condensation is bound to lead to oxazolidines. Davies,[9] Schmidt,[10] and Welsh [11] have already shown that both ephedrine and *ψ*-ephedrine give oxazolidines on reaction with benzaldehyde. Whilst di-*n*-butyl ketone, di*iso*butyl ketone, diethyl ketone, acetophenone, 4-methylacetophenone, and *p*-dimethylamino- and *p*-benzyloxy-benzaldehyde failed to react, condensation products were obtained with *cyclo*pentanone, *cyclo*hexanone, *m*-nitrobenzaldehyde, and dichloroacetaldehyde. Freudenberg and Geiger [12] recently described the condensation of acetone with (−)-ephedrine. Whilst for the condensation with the aldehydes azeotropic distillation with benzene was sufficient, the two ketones mentioned reacted only in boiling xylene and in presence of catalytic quantities of iodine.[6] As expected, the products showed the typical oxazolidine infrared spectrum; in some cases, four, not three, bands were observed in the expected region. For the *cyclo*pentanone derivative, the molecular refraction was determined; it showed the depression characteristic for five-membered rings of this type.[1]

Several of the oxazolidines derived from *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol have been tested for bacteriostatic or bactericidal activity against a strain of *E. coli*, which was inhibited to 50% by 2·5 μg. and completely by 5·0 μg. of chloroamphenicol per ml. None of the products, not even the dichloromethyl compound which resembles the natural antibiotic, showed any activity in doses of 2·5—50 μg./ml. This tends to show that for the action of the antibiotic an open structure of the side chain is essential.

Experimental

The condensations were carried out by azeotropic distillation of the components with benzene, unless indicated otherwise; in order to avoid autoxidation, an atmosphere of nitrogen was employed. Light petroleum had b. p. 60—80°, and ligroin, b. p. 90—120°. Most of the infrared spectra were determined in suspensions of the compounds in paraffin oil, by use of a Perkin-Elmer single beam instrument and a sodium chloride prism. The ultraviolet spectra were measured with a Beckman Quartz Spectrophotometer, with alcohol as solvent (figures in parentheses being log ε).

[8] Pedvazzoli, 14th Internat. Congr. Pure Appl. Chem., Zürich, 1955.
[9] Davies, *J.*, 1932, 1580.
[10] Schmidt, *Arch. Pharm.*, 1914, **252**, 89.
[11] Welsh, *J. Assoc. Offic. Agric. Chemists*, 1948, **31**, 528.
[12] Freudenberg and Geiger, *Annalen*, 1952, **575**, 145.

threo-2-*Dichloromethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine*.—A solution of *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (6·4 g., 0·03 mole) and dichloroacetaldehyde (3·4 g., 0·03 mole) in benzene (80 ml.) was refluxed azeotropically until the theoretical quantity of water had been collected. The solution was evaporated and the solid residue crystallised from methanol–ether, giving the *oxazolidine* as needles, m. p. 175—176° (Found : C, 42·8; H, 4·0; N, 9·0; Cl, 22·7. $C_{11}H_{12}O_4N_2Cl_2$ requires C, 43·0; H, 3·9; N, 9·1; Cl, 23·1%). Infrared bands at 3230 (primary OH), 1106, 1127, 1147 (oxazolidine), 1064 cm.$^{-1}$ (primary OH). Ultraviolet bands at 2320 (3·50), 2730 Å (4·22). Analogously, the following substances were prepared :

erythro-2-*Dichloromethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine* (from methanol), needles, m. p. 203—204° (Found : C, 42·8; H, 3·6; N, 8·8; Cl, 23·0. $C_{11}H_{12}O_4N_2Cl_2$ requires C, 43·0; H, 3·9; N 9·1; Cl, 23·1%). Infrared bands at 3210, 1110, 1134, 1168, 1945 cm.$^{-1}$. Ultraviolet bands at 2325 (3·51), 2740 Å (4·23).

threo-2 : 2-*Diethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine* (from methyl*cyclo*hexane), prisms, m. p. 124—125° (Found : C, 59·9; H, 6·8; N, 9·9. $C_{14}H_{20}O_4N_2$ requires C, 60·0; H, 7·1; N, 10·0%). Infrared bands at 3248, 1091, 1107, 1152, 1043 cm.$^{-1}$. Ultraviolet bands at 2345 (3·40), 2700 Å (4·00).

erythro-2 : 2-*Diethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine*. The viscous product crystallised when triturated at 0° with acetone–ligroin. Recrystallisation from the same mixture gave prismatic needles, m. p. 131—132° (Found : C, 59·8; H, 7·1; N, 10·1%). Infrared bands at 3255, in the oxazolidine region without fine structure, and at 1054 cm.$^{-1}$. Ultraviolet bands at 2325 (3·41), 2750 Å (4·10).

threo-4-*Hydroxymethyl*-5-p-*nitrophenyloxazolidine*-2-spiro*cyclohexane* (from acetone–ligroin), m. p. 107—108° (Found : C, 61·2; H, 6·6; N, 9·5. $C_{15}H_{20}O_4N_2$ requires C, 61·6; H, 6·8; N, 9·6%). Infrared bands at 3355, broad max. at 1127, and at 1027 cm.$^{-1}$. Ultraviolet bands at 2340 (3·50), 2750 Å (4·15).

erythro-4-*Hydroxymethyl*-5-p-*nitrophenyloxazolidine*-2-spiro*cyclohexane*. The product, triturated with alcohol and recrystallised from acetone–ligroin, had m. p. 125—126° (Found : C, 61·4; H, 6·8; N, 9·3%). Infrared spectrum as for the *threo*-isomer, but max. at 1056 instead of 1027 cm.$^{-1}$. Ultraviolet bands at 2325 (3·50) and 2730 Å (4·10).

threo-2-*Benzylideneamino*-1-p-*nitrophenylpropane*-1 : 3-*diol* (from methanol), m. p. 152—153° (Found : C, 64·0; H, 5·2; N, 9·0. $C_{16}H_{16}O_4N_2$ requires C, 64·0; H, 5·3; N, 9·3%). Strong infrared band at 1670 cm.$^{-1}$ (C=N).

threo-2 : 8-*Bisdichloromethyl*-4-p-*nitrophenyl*-3 : 7-*dioxa*-1-*aza*bicyclo[3 : 3 : 0]*octane* (III). Azeotropic distillation of a solution of *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (6·4 g.) and dichloroacetaldehyde (6·9 g.) for 4 hr. gave 2 mols. of water. The solid residue from the benzene solution was recrystallised from methanol–ether; this derivative melted at 193—198° (Found : C, 39·2; H, 3·3; N, 7·4; Cl, 34·9. $C_{12}H_{12}O_4N_2Cl_4$ requires C, 38·8; H, 3·0; N, 7·0; Cl, 35·3%). The erythro-*isomer* (from methanol) formed needles, m. p. 178—182° (Found : C, 39·3; H, 3·1; N, 7·2; Cl, 34·8%).

threo-N-cyclo*Hexylidenephenylserine ethyl ester*. *threo*-Phenylserine ethyl ester (m. p. 84—85°, from light petroleum) (3·1 g.) and *cyclo*hexanone (1·5 g.) were dissolved in toluene (70 ml.) and subjected to azeotropic distillation. Within 2 hr. the reaction was complete. From ether, containing a little methanol, crystals, m. p. 61—62°, of the cyclo*hexylidene derivative* (Found : C, 70·6; H, 7·8; N, 4·5. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·9; N, 4·8%) separated. Infrared bands at 1678 (C=N), 1720, 3180, 3380 cm.$^{-1}$ (hydroxyl).

Condensation of the *erythro*-ester was carried out in benzene and required 3 hr. The erythro-*product*, crystallised from ether containing a little methanol, had m. p. 64—65° and gave a large depression on admixture with its isomer (Found : C, 70·8; H, 7·6; N, 4·7%). Infrared bands at 1670, 1700, 3310 cm.$^{-1}$.

threo-N-*Benzylidenephenylserine ethyl ester* (obtained in benzene; 4 hr.) formed leaflets, m. p. 98—99°, from acetone–ligroin (Found : C, 72·3; H, 6·0; N, 4·6. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). Infrared bands at 1665, 3450 cm.$^{-1}$.

erythro-3 : 4-*Dimethyl*-5-*phenyloxazolidine*-2-spiro*cyclohexane*. The reaction between (±)-ephedrine (4·95 g.) and *cyclo*hexanone (5·94 g.) in boiling xylene (90 ml.), carried out in the presence of a small quantity of iodine, required 4 hr. for completion. The product solidified and crystallised from propan-2-ol in needles, m. p. 78—79° (55%) (Found : C, 78·1; H, 9·2; N, 5·7. $C_{16}H_{23}ON$ requires C, 78·4; H, 9·4; N, 5·7%). Infrared bands at 1067, 1087, 1125, 1149 cm.$^{-1}$. Ultraviolet bands at 2480 (3·41), 2590 Å (2·60).

erythro-3 : 4-*Dimethyl*-5-*phenyloxazolidine*-2-spiro*cyclopentane*. The reaction carried out as above, but without addition of iodine, required 7 hr. The *product* was an oil, b. p. 178—180°/

23 mm., 140—141°/3 mm, n_D^{25} 1·5240, d_4^{25} 1·0270, $[M]_D$, 68·70 (calc. 68·05) (yield, 22%) (Found : C, 77·5; H, 9·0; N, 5·8. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1; N, 6·0%). Infrared bands at 1070, 1128, 1142, 1174 cm.$^{-1}$. Ultraviolet bands at 2440 (2·25), 2650 Å (2·39).

erythro-3 : 4-*Dimethyl-2-m-nitrophenyl-5-phenyloxazolidine*. The reaction required 3 hr. in boiling benzene. The *product* formed needles, m. p. 75·5—76·5°, from light petroleum (Found : C, 68·2; H, 5·9; N, 9·2. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·0; N, 9·4%). Infrared bands at 1061, 1092, 1137, 1192 cm.$^{-1}$. Ultraviolet bands at 2310 (3·56), 2600 Å (3·90).

erythro-2-*Dichloromethyl*-3 : 4-*dimethyl-5-phenyloxazolidine*. Reaction in benzene required 4 hr., giving the *product* (from benzene–light petroleum), m. p. 207—208° (Found : C, 55·2; H, 5·4; N, 5·4; Cl, 27·0. $C_{12}H_{15}ONCl_2$ requires C, 55·4; H, 5·7; N, 5·4; Cl, 27·3%). Infrared bands at 1091, 1133, 1158 cm.$^{-1}$. Ultraviolet bands at 2325 (1·82), 2575 Å (1·40). For comparison, the spectrum of (±)-ephedrine was determined in EtOH, *viz.*, 2400 (1·78), 2590 Å (2·26).

The infrared spectra were measured by Dr. S. Pinchas, Weizmann Institute of Science, Rehovoth, the ultraviolet spectra by Mr. Ch. Eger of this Department.

Scientific Department, Ministry of Defence,
Tel-Aviv, Israel. [*Received, November 23rd*, 1955.]

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330. *Diaryl-2 : 2′-disulphonic Acids and Related Compounds. Part I. The Diphenyl and the Ditolyl Series.*

By W. L. F. Armarego and E. E. Turner.

Syntheses of derivatives of diphenyl-2 : 2′-disulphonic acid are more surely based on Ullmann reactions with phenyl *o*-iodobenzenesulphonate than on the Barber–Smiles process of heating the alkali *o*-iodobenzenesulphonate with copper in aqueous copper sulphate. The reductive scission of 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonyl dichloride into *m*-mercaptotoluene recorded by Barber and Smiles [1] is shown to be illusory.

The optical resolution of diphenyl-2 : 2′-disulphonic acid,[2] whilst contributing much to our knowledge of the relation between steric effects and optical stability, left unsolved a number of problems, to the solution of which the present investigations are addressed.

The formation of sodium diphenyl-2 : 2′-disulphonate by the action of copper powder on a boiling aqueous solution of sodium *o*-iodobenzenesulphonate and copper sulphate is not uniformly successful. Although the diphenyl derivative is formed, some of the iodosulphonate remains unchanged and some is de-iodinated. A surer way into the series is now found to be by the action of copper on phenyl *o*-iodobenzenesulphonate, which is readily obtained from *o*-iodobenzenesulphonyl chloride. The diphenyl diphenyl-2 : 2′-disulphonate formed is with difficulty hydrolysed by acid, but is converted by boiling alcoholic sodium ethoxide into the sodium disulphonate. It may be noted that Ferns and Lapworth,[3] by the action of one mol. of sodium ethoxide on phenyl toluene-*p*-sulphonate, obtained phenetole as one product, the process being expressed as follows :

$$C_7H_7{\cdot}SO_3Ph + NaOEt = C_7H_7{\cdot}SO_3Et + NaOPh$$
$$C_7H_7{\cdot}SO_3Et + NaOPh = C_7H_7{\cdot}SO_3Na + PhOEt$$

We find that if two mols. of sodium ethoxide are used no phenetole is detectable. Probably in this case the second reaction is :

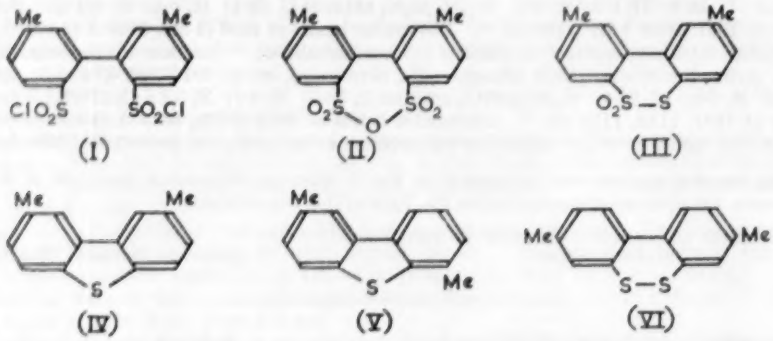
$$C_7H_7{\cdot}SO_3Et + NaOEt = C_7H_7{\cdot}SO_3Na + Et_2O$$

Barber and Smiles [1] reduced diphenyl-2 : 2′-disulphonyl dichloride to 2 : 2′-dimercaptodiphenyl, which was oxidised by aqueous-alcoholic ferric chloride to the cyclic disulphide. We find that the latter is formed by the action of hydriodic acid in acetic acid on the

[1] Barber and Smiles, *J.*, 1928, 1141.
[2] Lesslie and Turner, *J.*, 1932, 2394.
[3] Ferns and Lapworth, *J.*, 1912, **101**, 279.

disulphonyl dichloride, and that the disulphide, and the cyclic thiolsulphonate obtained from it by oxidation,[1] both give dibenzothiophen when they are heated with copper powder.

By the deamination of *o*-tolidine-6 : 6′-disulphonic acid (cf. Limpricht [4] and Helle [5]) 5 : 5′-dimethyldiphenyl-2 : 2′-disulphonic acid is obtainable. The sodium salt of this acid



is now found to react with a mixture of phosphorus pentachloride and phosphoryl chloride to give approximately equivalent quantities of the disulphonyl dichloride (I) and the disulphonic anhydride (II). The disulphonyl dichloride is reduced by zinc and acid to the 2 : 2′-dithiol, an alkaline solution of which reacts with 1-chloro-2 : 4-dinitrobenzene to give the di-(2 : 4-dinitrophenyl sulphide). The dithiol is readily oxidised to the cyclic disulphide, which is also formed from (I) and (II) by reduction with hydriodic–acetic acid. Both (I) and (II) are converted by aqueous alkaline alkali sulphite, followed by acidification, into the cyclic thiolsulphonate (III) which is also obtainable by oxidation of the cyclic disulphide. This disulphide, when heated with copper, passes into a dimethyldibenzothiophen which could be either (IV) or (V). The product is identical with that formed through the diazo-derivative of 2-amino-4 : 4′-dimethyldiphenyl sulphide and is therefore (IV). The two specimens of cyclic sulphide (IV) of different origin were oxidised to identical sulphones. 2 : 2′-Dihydroxy-5 : 5′-dimethyldiphenyl was obtained by demethylating its dimethyl ether, but it could not be converted into a dibenzothiophen by the action of phosphorus pentasulphide (cf. Gilman and Jacoby [6]).

By heating phenyl 4-iodotoluene-3-sulphonate with copper, phenyl 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonate is obtained. This ester is converted by boiling *n*-butanolic sodium *n*-butoxide into sodium 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonate, and the latter, with phosphorus pentachloride, gives 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonyl dichloride, m. p. 183—184°, not 117—118° as stated by Barber and Smiles. According to these authors, the disulphonyl dichloride was reduced by zinc and acid to *m*-mercaptotoluene. This seemed to us to be totally at variance with our knowledge of the 1 : 1′-diaryl linking, and we have re-examined the compounds concerned. The action of copper on a boiling aqueous solution containing copper sulphate and sodium 4-iodotoluene-3-sulphonate does not give appreciable quantities of sodium 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonate. The bulk of the material is unchanged and the rest is convertible by phosphorus pentachloride into 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonyl dichloride and toluene-*m*-sulphonyl chloride. The latter is evidently the source of the *m*-mercaptotoluene which Barber and Smiles isolated. We find that the dimethyldisulphonyl dichloride can in fact be reduced to a dithiol, which however readily undergoes oxidation to the cyclic disulphide (VI). An alkaline solution of the dithiol reacts with 1-chloro-2 : 4-dinitrobenzene to give the di-(2 : 4-dinitrophenyl sulphide). When heated with copper bronze, the cyclic disulphide (VI) gives 2 : 7-dimethyldibenzothiophen.

[4] Limpricht, *Annalen*, 1891, **261**, 310.
[5] Helle, *ibid.*, 1892, **270**, 359.
[6] Gilman and Jacoby, *J. Org. Chem.*, 1938, **3**, 109.

Experimental

Diphenyl-2 : 2′-disulphonyl Dichloride.—The procedure of Barber and Smiles [1] was modified to the following.

To a boiling, stirred solution of sodium *o*-iodobenzenesulphonate (20 g.) in water (100 ml.) containing 1 ml. of 5% copper sulphate solution copper bronze (12 g.) was added. After 2½ hr. the mixture was filtered. The filtrate was evaporated to dryness and the white residue was dried at 120—130° and treated with an equal weight of phosphorus pentachloride. Benzenesulphonyl chloride was identified by conversion into benzenesulphonamide, m. p. 153°. The diphenyl-2 : 2′-disulphonyl dichloride, crystallised from glacial acetic acid, had m. p. 142—144° (Limpricht gives m. p. 138°) (yield, 2·9 g., 12% calc. on the iodo-salt).

Diphenyl Diphenyl-2 : 2′-disulphonate.—(*a*) The sulphonyl chloride (1·1 g., 1 mol.) in dry pyridine (10 ml.) was heated with phenol (1·2 g., 4 mols.). The ester obtained in the usual manner crystallised from ethanol in needles, m. p. 127—128° (0·4 g., 28%).

(*b*) *o*-Iodobenzenesulphonyl chloride (132 g., 1 mol.) was heated with phenol (2 mols.) and sodium carbonate (1½ mols.) on a boiling-water bath for 1 hr. *Phenyl o-iodobenzenesulphonate* crystallised from ethanol in needles, m. p. 93—94° (142 g., 92%) (Found : C, 40·3; H, 2·4; I, 35·4; S, 8·8. $C_{12}H_9O_3IS$ requires C, 40·0; H, 2·5; I, 35·2; S, 8·9%).

This ester (133 g.) was heated in a metal bath at 180—190°, and an equal weight of copper bronze was added at such a rate as to keep the temperature below 210°. This reaction was vigorous. The *diphenyl ester* was extracted with *o*-dichlorobenzene, and the product obtained by concentration. It crystallised from ethanol in needles, m. p. 127—128° (70 g., 81%) (Found : C, 61·6; H, 3·8; S, 13·6. $C_{24}H_{18}O_4S_2$ requires C, 61·8; H, 3·9; S, 13·7%).

Hydrolysis.—Diphenyl diphenyl-2 : 2′-disulphonate (9·4 g., 1 mol.), in absolute ethanol (200 ml.), was treated with a solution of sodium (1·84 g., 4 atoms) in ethanol (150 ml.). The mixture was boiled under reflux for 2 hr.; separation of solid was then complete. This was filtered off and dissolved in water (100 ml.), the solution was acidified with dilute hydrochloric acid, and phenol extracted with ether. The aqueous layer, after careful neutralisation with 10% aqueous sodium hydroxide, was evaporated to dryness. The residue (4·8 g.) with phosphorus pentachloride gave a disulphonyl dichloride (43%), m. p. 143—144°, mixed m. p. 142—143°.

2 : 2′-*Diphenylene Disulphide* (*Dibenzo-o-dithiin*).—Diphenyl-2 : 2′-disulphonyl dichloride (0·9 g.) in hot glacial acetic acid (10 ml.) was added to 55% w/w hydriodic acid (20 ml.), and the solution left at room temperature for 24 hr. The solid that separated was washed with aqueous sulphur dioxide; it crystallised from glacial acetic acid as yellow needles (0·4 g., 55%), m. p. 113—114° alone or mixed with the disulphide obtained by oxidation of the dithiol with ferric chloride.

Dibenzothiophen from "Diphenyl-2 : 2′-thiolsulphonate" (*Dibenzo-o-dithiin 5 : 5-Dioxide*; Ring Index No. 1936).—The thiolsulphonate (1 g.) was heated with copper bronze (2 g.) at 250° for 2 hr. Extraction with ethanol gave dibenzothiophen (0·5 g., 63%), m. p. 100°. The mixed m. p. with dibenzothiophen obtained by similar treatment of 2 : 2′-diphenylene disulphide was 98—100°. The thiolsulphonate was obtained from the disulphide in 60% yield by oxidation with concentrated nitric acid in acetic acid.

Disodium 5 : 5′-Dimethyldiphenyl-2 : 2′-disulphonate.—This was prepared by a modification of the method used by Limpricht [4] for diphenyl-2 : 2′-disulphonic acid. *o*-Tolidine-6 : 6′-disulphonic acid (111·6 g., 1 mol.) was suspended in water (600 ml.) and neutralised with a solution of sodium hydroxide (16 g. in 20 ml. of water). Diazotisation was carried out between −5° and −2° since the tetrazo-salt decomposed rapidly above −2°. Sodium nitrite (60 g., 1 mol.) in water (150 ml.) was added to the cold solution, and was followed slowly by dilute sulphuric acid (concentrated acid, 120 ml., and ice 600 g.). The tetrazo-salt that separated was kept at −5° for 1 hr., then rapidly filtered off, dried between filter paper, and added to absolute ethanol (600 ml.). On addition of copper bronze (1 g.) the tetrazo-salt decomposed. The alcohol was then distilled off and the residue dissolved in water (800 ml.), neutralised with 10% aqueous sodium hydroxide, boiled with charcoal, filtered, and concentrated. On cooling, the sodium salt crystallised in plates (yield of anhydrous salt, 88 g., 68%).

5 : 5′-Dimethyldiphenyl-2 : 2′-disulphonyl Dichloride and -2 : 2′-disulphonic Anhydride.—Sodium 5 : 5′-dimethyldiphenyl-2 : 2′-disulphonate (88 g., 1 mol.) was ground with phosphorus pentachloride (94 g., 2 mols.). The mixture did not melt when heated on a boiling-water bath, and phosphoryl chloride (25 ml.) was added and the mixture heated in a metal-bath at 130° under a condenser for 1 hr. The yellow pasty product was decomposed with ice-water, filtered

off, dried, and dissolved in hot benzene. On cooling, the *anhydride* crystallised in rhombic crystals, m. p. 234—235° (18 g., 27%) (Found: S, 19·5. $C_{14}H_{12}O_5S_2$ requires S, 19·8%). The mother-liquor was concentrated to a small volume by distilling off the benzene at a low temperature in a vacuum. The *disulphonyl dichloride* crystallised in needles (24 g., 28%), m. p. 227—228° (mixed m. p. with anhydride, 195—199°) (Found: S, 17·1. $C_{14}H_{12}O_4Cl_2S_2$ requires S, 16·9%). Both substances were recrystallised from acetic anhydride.

Diphenyl 5 : 5′-*Dimethyldiphenyl*-2 : 2′-*disulphonate*.—This was prepared in the usual manner from the anhydride or disulphonyl dichloride but with dry pyridine instead of sodium carbonate; with the latter the original material was always hydrolysed to the disulphonic acid. The *ester* crystallised from *n*-butanol in needles, m. p. 189—191° (Found: S, 13·2. $C_{26}H_{22}O_6S_2$ requires S, 12·9%).

5 : 5′-*Dimethyldiphenyl*-2 : 2′-*disulphonanilide*.—This *dianilide* was obtained in the usual manner from the dichloride, and crystallised from *n*-butanol in needles (27%), m. p. 234—236° (decomp.) (Found: S, 12·9. $C_{26}H_{24}O_4N_2S_2$ requires S, 13·0%).

" 5 : 5′-*Dimethyldiphenyl*-2 : 2′-*thiolsulphonate* " (2 : 9-*dimethyldibenzo*-o-*dithiin* 5 : 5-*dioxide*) (III) was obtained by shaking the anhydride with alkaline sulphite for 6 hr. at 80—100°, and then strongly acidifying the solution with dilute mineral acid. It crystallised from *n*-butanol in needles, m. p. 146—147° (45%) (Found: S, 23·2. $C_{14}H_{12}O_3S_2$ requires S, 23·2%). Similar results were obtained with the disulphonyl dichloride.

5 : 5′-*Dimethyl*-2 : 2′-*diphenylene Disulphide* (2 : 9-*Dimethyldibenzo*-o-*dithiin*).—5 : 5′-Dimethyldiphenyl-2 : 2′-disulphonyl dichloride (7·6 g.) in boiling glacial acetic acid (120 ml.) was treated with 55% (w/w) hydriodic acid (80 ml.). An oil separated which on cooling solidified. It crystallised from glacial acetic acid in golden-yellow plates, m. p. 88—89° (3·3 g., 69%). Under similar conditions the anhydride gave the disulphide, m. p. and mixed m. p. 89—90°, in 53% yield.

Oxidation. The disulphide (1 g.) in boiling glacial acetic acid (15 ml.) was slowly treated with concentrated nitric acid (20 ml.). The solution was kept for 3 hr. but no solid separated. The mixture was poured into water (100 ml.) and the white thiolsulphonate that separated was filtered off and dried; it crystallised from *n*-butanol as needles, m. p. and mixed m. p. 144—146° (0·2 g., 42%).

5 : 5′-*Dimethyldiphenyl*-2 : 2′-*dithiol and the* 2 : 2′-*Di*-(2 : 4-*dinitrophenyl Sulphide*).—A solution of 5 : 5′-dimethyldiphenyl-2 : 2′-disulphonic anhydride (7·6 g.) in boiling glacial acetic acid (300 ml.) was rapidly cooled to 15° in order to avoid hydrolysis. Zinc dust (12 g.) was added, followed by concentrated hydrochloric acid (20 ml.). The acid was added at such a rate as to keep the temperature below 20°. Then the mixture was heated on a boiling-water bath until all the metal had dissolved. The solution was concentrated to 150 ml. *in vacuo*, poured into water (400 ml.), and acidified with 2N-hydrochloric acid (400 ml.). The oil which separated was steam-distilled, and the distillate extracted with ether, dried ($CaCl_2$), and freed from ether. The oily residue had an unpleasant odour and did not solidify. This was the dithiol as it was freely soluble in alkali. It was dissolved in ethanol (15 ml.), made alkaline with 10% aqueous sodium hydroxide (2 ml.), and mixed with a solution of 1-chloro-2 : 4-dinitrobenzene (2 g.) in ethanol (10 ml.). The yellow solid *disulphide* suddenly separated. It crystallised from large volumes of *n*-butanol in golden-yellow needles, m. p. 230—231° (0·9 g., 20%) (Found: S, 11·3. $C_{26}H_{16}O_8N_4S_2$ requires S, 11·1%).

The above reduction was repeated but with the disulphonyl dichloride, and the oily dithiol on oxidation with alcoholic ferric chloride gave 5 : 5′-dimethyl-2 : 2′-diphenylene disulphide in 20% yield.

2 : 8-*Dimethyldibenzothiophen* (Ring Index No. 1743).—(*a*) 5 : 5′-Dimethyl-2 : 2′-diphenylene disulphide (2 g.) was thoroughly mixed with copper bronze (2 g.) and heated at 250—260° for 1½ hr. The residue was distilled in a vacuum and the distillate crystallised, on cooling, to needles of the *dibenzothiophen* which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 121—122° (1·4 g., 80%) (Found: S, 15·3. $C_{14}H_{12}S$ requires S, 15·1%).

(*b*) (cf. Cullinane, C. Davies, and G. Davies [7] for the similar synthesis of 2-nitrodibenzothiophen.) 4 : 4′-Dimethyl-2-nitrodiphenyl sulphide was prepared in the usual manner from 4-bromo-3-nitrotoluene, 4-mercaptotoluene and sodium ethoxide. The base obtained by reduction of the nitro-sulphide with tin and hydrogen chloride was an oil and was converted directly into the thiophen (yield, 0·5 g., 11%), m. p. 120—121°; mixed m. p. with above thiophen 119—120°.

2 : 8-*Dimethyldibenzothiophen* 1 : 1-*Dioxide*.—2 : 8-Dimethyldibenzothiophen (0·25 g., from

[7] Cullinane, Davies, and Davies, *J.*, 1936, 1435.

the disulphide) in boiling glacial acetic acid (20 ml.) was oxidised with excess of 3% aqueous potassium permanganate. The product was poured into water and decolorised with sodium metabisulphite, and the white precipitate filtered off. It crystallised in needles (from glacial acetic acid), m. p. 297—298° (0·2 g., 71%). The *dioxide* obtained in a similar manner from the thiophen derived from the nitro-sulphide melted at 298—299° (mixed m. p. 297—298°) (Found: C, 69·0; H, 5·1; S, 12·9. $C_{14}H_{12}O_2S$ requires H, 69·0; S, 4·9; 13·1%).

Phenyl 2-Iodo-5-methylbenzenesulphonate.—2-Iodo-5-methylbenzenesulphonyl chloride (148 g., 1 mol.) was heated as usual with phenol (2 mols.) and sodium carbonate (1½ mols.). The *ester* crystallised from ethanol in prisms, m. p. 87—88° (164 g., 94%) (Found: S, 8·9. $C_{13}H_{11}O_3IS$ requires S, 8·6%).

Diphenyl 4 : 4′-Dimethyldiphenyl-2 : 2′-disulphonate.—Phenyl 2-iodo-5-methylbenzenesulphonate (122 g.) was heated in a bath at 180—190° and copper bronze (100 g.) added slowly, the temperature being kept below 210°. The reaction was vigorous. By extraction with chlorobenzene and concentration, the *ester* was obtained crystalline. It crystallised from *n*-butanol in flakes, m. p. 146—147° (97 g., 92%) (Found: S, 13·2. $C_{26}H_{22}O_6S_2$ requires S, 12·9%).

Disodium 4 : 4′-Dimethyldiphenyl-2 : 2′-disulphonate.—The phenyl ester (1 mol.) was hydrolysed with sodium *n*-butoxide (4 mol.) in boiling *n*-butanol in 3 hr. The product was isolated in 96% yield by distilling off the alcohol, as in the previous hydrolysis.

4 : 4′-Dimethyldiphenyl-2 : 2′-disulphonyl Dichloride.—This was obtained from the above salt with the calculated quantity of phosphorus pentachloride. It crystallised from glacial acetic acid in needles (52%), m. p. 183—184° (Barber and Smiles gave m. p. 118°) (Found: S, 17·3. $C_{14}H_{12}O_4S_2Cl_2$ requires S, 16·9%). The phenyl ester obtained by heating this substance with phenol in pyridine was identical with diphenyl 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonate. The *disulphonanilide* crystallised from *n*-butanol in needles, m. p. 205—206° (Found: S, 13·1. $C_{26}H_{24}O_4N_2S_2$ requires S, 13·0%).

When sodium 4-iodo-3-methylbenzenesulphonate (20 g.) in water (100 ml.) containing 5% copper sulphate solution (1 ml.) was boiled under reflux and stirred mechanically for 3 hr., three substances were isolated: (i) sodium 4-iodo-3-methylbenzenesulphonate (13 g. anhyd., 65%), (ii) sodium 4 : 4′-dimethyldiphenyl-2 : 2′-disulphonate, and (iii) sodium toluene-*m*-sulphonate. The last two substances were converted into the corresponding sulphonyl chlorides. 4 : 4′-Dimethyldiphenyl-2 : 2′-disulphonyl chloride (2·2 g., 19% calc. on original iodo-salt) melted at 183—185° alone or mixed with the sulphonyl chloride obtained *via* the Ullmann reaction.

4 : 4′-Dimethyl-2 : 2′-diphenylene disulphide (*3 : 8-dimethyldibenzo-o-dithiin*) was obtained by the action of hydriodic acid (*d* 1·7) on the sulphonyl chloride in boiling glacial acetic acid. It crystallised from ethanol in yellow needles (81%), m. p. 114—115° (Found: C, 68·6; H, 4·9. $C_{14}H_{12}S_2$ requires C, 69·0; H, 4·9%).

" *4 : 4′-Dimethyldiphenyl-2 : 2′-thiolsulphonate* " (*3 : 8-dimethyldibenzo-o-dithiin 5 : 5-dioxide*) was prepared in 75% yield in a way similar to that used for its isomer. It crystallised from *n*-butanol in needles, m. p. 170—171° (Found: C, 60·1; H, 4·7; S, 23·5. $C_{14}H_{12}O_2S_2$ requires C, 60·8; H, 4·4; S, 23·2%).

4 : 4′-Dimethyldiphenyl-2 : 2′-dithiol.—This was obtained by reducing the corresponding disulphonyl dichloride with zinc and hydrochloric acid in ethanol as in the case of the 3 : 3′-dimethyl compound. The dithiol (an oil) was not steam-distilled as it was oxidised readily to the cyclic disulphide in 63% yield. The *di-(2 : 4-dinitrophenyl sulphide)* crystallised from a large volume of *n*-butanol in canary-yellow needles, m. p. 236—237° (yield, 63%) (Found: N, 9·6. $C_{26}H_{18}O_8N_4S_2$ requires N, 9·7%).

3 : 7-Dimethyldibenzothiophen, obtained by the method used for its isomer, had b. p. 186°/10 mm. (yield 92%). The distillate crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 151—152° (Found: C, 79·2; H, 5·9; S, 14·8. $C_{14}H_{12}S$ requires C, 79·9; H, 5·7; S, 15·1%).

Di-o-iodophenyl Disulphoxide (*o-Iodophenyl o-Iodobenzenethiolsulphonate*).—*o*-Iodobenzenesulphonyl chloride (6 g.) was reduced with sodium sulphite solution (15 g. of hydrated salt in 50 ml. of water) made alkaline with 10% sodium hydroxide solution (15 ml.). After being heated on a boiling-water bath for 15 min. the sulphonyl chloride dissolved. The resulting yellow solution gave *o*-iodobenzenesulphinic acid, on acidification, as needles, m. p. 112° (Barber and Smiles [1] gave m. p. 108°). The *thiolsulphonate* was isolated after the sulphinic acid had been heated for 2 hr. on a boiling-water bath in excess of dilute sulphuric acid; it crystallised from ethanol in needles (3·2 g.), m. p. 158—159° (Found: I, 51·0. $C_{12}H_8O_2S_2I_2$ requires I, 50·6%).

Di-o-iodophenyl Disulphide.—*o*-Iodobenzenesulphonyl chloride (3 g., 1 mol.) in hot glacial acetic acid (20 ml.) was treated with hydriodic acid (20 ml., 10 mols.) and left at room temperature for 24 hr. The disulphide separated and crystallised from a large quantity of glacial acetic acid in prisms (1·4 g., 83%), m. p. 135—136° (Barber and Smiles [1] give m. p. 133°).

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331. *The Preparation of Nitrosoalkanes from Alkyl Nitrites.*

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Every possible C_1—C_4 and one C_5 nitrosoalkane has been prepared pyrolytically from alkyl nitrites in a flow system, and the *cis*-dimers have been isolated except that of 2-methyl-2-nitrosopropane where sterically only the *trans*-dimer is possible. *trans*-Dimers have been detected in the products resulting when the *cis*-dimer is heated, and in two cases the *trans*-dimer has been isolated. Nitrosoalkane dimers have been detected in the products formed by photolyses of alkyl nitrites. The ultraviolet and infrared absorption spectra and other properties of the dimers are discussed, and possible mechanisms for the pyrolyses of alkyl nitrites are formulated.

DIMERIC nitrosoalkanes have been either isolated [1,2] or detected [2] in the photolysis products of some alkyl nitrites. Dimeric 4-nitrosoheptane has been isolated from the photolysis products of *n*-heptane, nitric oxide, and chlorine mixtures, the reaction sequence being :

$$n\text{-}C_7H_{16} + Cl \longrightarrow (C_3H_7)_2CH\cdot + HCl$$
$$(C_3H_7)_2CH\cdot + NO \longrightarrow (C_3H_7)_2CH\cdot NO$$

The chlorine atoms are produced photolytically from chlorine. A recent study of the pyrolysis and photolysis of *tert.*-butyl nitrite [4] has shown that there are two different dimers of nitrosomethane, geometrical isomerism being the most probable explanation of the properties reported. Although photolysis of a number of alkyl nitrites yielded nitrosomethane or unidentified nitrosoalkanes,[2] it has been generally assumed [5] that thermal decomposition of alkyl nitrites is best represented by the equation :

$$R\cdot CH_2\cdot O\cdot NO \longrightarrow \tfrac{1}{2}R\cdot CHO + \tfrac{1}{2}R\cdot CH_2\cdot OH + NO$$

the initial reaction being :

$$R\cdot CH_2\cdot O\cdot NO \longrightarrow R\cdot CH_2\cdot O\cdot + NO$$

subsequent reactions of the alkoxy-radicals producing the alcohol and aldehyde by a non-chain mechanism. The majority of the studies have been made by static methods with pressures of the order of 100 mm., reaction temperatures of about 200°, and reaction times of several minutes. With the possible exception of methyl nitrite,[6] the equations quoted have little or no quantitative significance : in other cases,[7] even qualitative identification of the aldehyde and/or alcohol is at best sketchy, and the amount of nitric oxide obtained was only 50—67% of that expected from the amount of nitrite decomposed. Rice and Rodowskas [8] have suggested that the nitric oxide produced in the primary decomposition

[1] Coe and Doumani, *J. Amer. Chem. Soc.*, 1948, **70**, 1516.
[2] Tarte, *Bull. Soc. roy. Liège*, 1953, **22**, 26.
[3] Müller and Metzger, *Chem. Ber.*, 1955, **88**, 165.
[4] Gowenlock and Trotman, *J.*, 1955, 4190.
[5] Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, 1954, p. 239.
[6] Steacie and Shaw, *Proc. Roy. Soc.*, 1934, *A*, **146**, 388.
[7] (*a*) Carter and Travers, *ibid.*, 1937, *A*, **156**, 495; (*b*) Gray, *ibid.*, 1954, *A*, **221**, 462; (*c*) Steacie and Shaw, *J. Chem. Phys.*, 1934, **2**, 345; 1935, **3**, 344; *Proc. Roy. Soc.*, 1935, *A*, **151**, 685; Steacie and Smith, *J. Chem. Phys.*, 1936, **4**, 504; Levy, *J. Amer. Chem. Soc.*, 1954, **76**, 3254.
[8] Rice and Rodowskas, *J. Amer. Chem. Soc.*, 1935, **57**, 350.

can remove free alkyl radicals resulting from the decomposition of alkoxy-radicals, a nitrosoalkane being formed :

$$R{\cdot}CH_2{\cdot}O \longrightarrow R{\cdot} + CH_2O$$
$$R{\cdot} + NO \longrightarrow R{\cdot}NO$$

Experimental

With the exception of *iso*pentyl nitrite, which was available commercially, all nitrites were prepared by the action of nitrous acid on the corresponding alcohol at 0°. The alcohols were commercial products apart from hexan-2-ol, 3-methylpentan-2-ol, and 3 : 3-dimethylbutan-2-ol which were prepared from acetaldehyde and the appropriate Grignard reagent. The nitrites were purified by bulb-to-bulb distillation *in vacuo* and pyrolyzed in the apparatus used for *tert.*-butyl nitrite [4] with the reaction vessel at 320°. Nitrites that yielded nitrosomethane were decomposed in the presence of nitrogen (used as a carrier gas), whereas other nitrites were decomposed in the absence of a carrier gas by pumping the nitrite vapour through the reaction vessel; optimum yields were the criterion of technique employed. Decomposition products and undecomposed nitrites were trapped at either −78° or −183°. During every decomposition an increase in pressure was observed; admission of air to the apparatus gave brown vapours, indicating that this increase was due, in part or in whole, to nitric oxide which is not completely condensed in liquid oxygen. The cooled traps contained solids coloured from yellow-brown to blue-green. In addition, undecomposed nitrites and carbonyl compounds were also trapped as white solids. On warming to room temperature, the undecomposed nitrites and carbonyl compounds other than polymeric formaldehyde melted to faintly yellow liquids : the coloured solids melted to liquids of the same colour which rapidly changed to white solids (cf. refs 4, 9). The nitrosoalkane from *iso*hexyl nitrite was of low vapour pressure and condensed to give a white solid above the level of the acetone in the −78° bath that surrounded the trap. When polymeric formaldehyde was deposited in the cooled trap, it was always separated from the nitrosoalkane deposit by a few cm., the $(CH_2O)_n$ deposit being nearer to the bottom of the trap. The undecomposed nitrite and volatile carbonyl compound were pumped off from the solid nitrosoalkane dimer and trapped in a receiver cooled in liquid oxygen. Volatile carbonyl compounds proved to be either acetone or acetaldehyde and were identified as the semicarbazone or dimethone respectively. Polymeric formaldehyde was removed from the trap wall by a spatula; it had m. p. 170° and a dimethone derivative was prepared. M. p.s and mixed m. p.s were : acetone semicarbazone, 187°; acetaldehyde dimethone, 140°; formaldehyde dimethone, 189°. Dimeric nitrosoalkanes were purified from any isomeric oxime either by dissolution in ethanol, rapid cooling to −78°, and filtration of the white solid formed or, where high solubility in ethanol at −78° made this impossible, by shaking with ether at −30°, filtration, and washing with cold (−30°) ether. In both cases, white crystalline solids resulted; it was necessary to pump off all traces of solvent under a vacuum. The identified pyrolysis products are given in Table 1. The dimeric nitrosoalkanes prepared by the above techniques are, with one exception,

Table 1. *Pyrolysis products of alkyl nitrites.*

Nitrite	CO compound	Nitrosoalkane	Nitrite	CO compound	Nitrosoalkane
Et	$(CH_2O)_n$	Me·NO	CHMePr^n	Me·CHO	Pr^n·NO
Pr^n *	$(CH_2O)_n$	Et·NO	CMe_2Et	$COMe_2$	Et·NO
Pr^i *	Me·CHO	Me·NO	CHMeBu^n	Me·CHO	Bu^n·NO
Bu^n *	$(CH_2O)_n$	Pr^n·NO	CHMeBu^i	,,	Bu^i·NO
Bu^s *	Me·CHO	Et·NO	CHMeBu^s	,,	Bu^s·NO
Bu^i *	$(CH_2O)_n$	Pr^i·NO	CHMeBu^t	,,	Bu^t·NO
Bu^t [4]	$COMe_2$	Me·NO	$CHEt_2{\cdot}CH_3$	$(CH_2O)_n$	C_5H_{11}·NO (probably $CHEt_2{\cdot}NO$)
Bu$^n{\cdot}CH_3$	$(CH_2O)_n$	Bu^n·NO			
Bu$^i{\cdot}CH_3$	$(CH_2O)_n$	Bu^i·NO			

* Adler, Pratt, and Gray (***Chem. and Ind.***, 1955, 1517) have recently isolated the same carbonyl compounds by pyrolysis of nitrites so marked.

cis-dimers, $\lambda_{max.}$ (in H_2O) varying from 265 to 271 mμ; the exception is dimeric 2-methyl-2-nitrosopropane, $\lambda_{max.}$ (in H_2O) 287 mμ. For a detailed summary of ultraviolet spectra see p. 1673. The detailed results for the *cis*-dimeric ***nitrosoalkanes*** are given in Table 2 : apart from *cis*-dimeric nitrosomethane [4] all are new compounds. Molecular weights were determined cryoscopically in benzophenone.

[5] Chilton and Gowenlock, *J.*, 1953, 3232; 1954, 3174.

TABLE 2. cis-*Dimeric nitrosoalkanes.*

Compound	M. p.	Found C (%)	Found H (%)	Found N (%)	Found *M*	Required C (%)	Required H (%)	Required N (%)	Required *M*
$(CH_3{\cdot}NO)_2$	97·5°	27·0	6·5	29·4	92	26·7	6·7	31·1	90
$(C_2H_5{\cdot}NO)_2$	84	40·6	8·5	22·8	118	40·7	8·5	23·7	118
$(n\text{-}C_3H_7{\cdot}NO)_2$	76	49·4	9·7	18·9	147	49·3	9·7	19·2	146
$(iso\text{-}C_3H_7{\cdot}NO)_2$	60	49·0	9·7	19·0	148	49·3	9·7	19·2	146
$(n\text{-}C_4H_9{\cdot}NO)_2$	72	55·3	10·3	16·1	166 *	55·2	10·4	16·1	174
$(iso\text{-}C_4H_9{\cdot}NO)_2$	80	54·9	10·7	15·8	171	55·2	10·4	16·1	174
$(sec.\text{-}C_4H_9{\cdot}NO)_2$	61	54·9	10·3	15·9	162 *	55·2	10·4	16·1	174
$(C_5H_{11}{\cdot}NO)_2$	42	59·2	10·9	13·5	192 *	59·4	11·0	13·9	202

* Faint blue colour appeared during determination.

Conversion of cis-*Dimers into* trans-*Dimers.*—The method established for nitrosomethane[4] (dissolution of the *cis*-dimer in chloroform, warming, and recrystallisation) was inapplicable to other nitrosoalkanes owing to the production of monomer (blue colour) in chloroform, with subsequent production of the oxime; in addition, the *trans*-dimers were very soluble in chloroform. The following method was therefore employed. The *cis*-dimer was rapidly heated to a few degrees above the m. p. and then cooled rapidly to room temperature. This process was then repeated two or three times. The resultant white solid was dissolved in a few ml. of ether and cooled to −78°, whereupon a white solid was deposited. This was rapidly filtered off in the cold and washed with cold (−78°) ether. The white solid was then allowed to warm to room temperature, whereupon in most cases it changed to a liquid (either melting or dissolving in traces of ether) below room temperature. Stable white solids were formed in two cases, *viz.*, *trans*-dimeric 2-*nitrosopropane*, m. p. 52° [Found: C, 48·8; H, 9·5; N, 19·0%; *M* (cryoscopic in benzophenone), 143. C_3H_7ON requires C, 49·3; H, 9·7; N, 19·2%; *M* 146]. and *trans*-dimeric 2-*methyl*-1-*nitrosopropane*, m. p. 40° [Found: C, 54·4; H, 10·1; N, 15·9%; *M* (cryoscopic in benzophenone), 176. C_4H_9ON requires C, 55·2; H, 10·4; N, 16·1%; *M* 174]. The liquid products were not analysed. *trans*-Dimeric 2-methyl-2-nitrosopropane was isolated by the purification technique used for *cis*-dimers; it had m. p. 70° (lit.,[11] disappears at 76°).

Ultraviolet Absorption Spectra.—Absorption spectra were measured as for nitrosomethane;[4] the solvents were water, ethanol, ether, and carbon tetrachloride. Organic solvents produce the *trans*-dimer from the *cis*-dimer,[4] this reaction being so rapid in carbon tetrachloride and ether that only $\lambda_{max.}$ of the *trans*-dimer could be observed. In ethanolic solution, the $\lambda_{max.}$ value for *cis*-dimers increased with time and consequently speedy measurement was essential. The rate of isomerisation varied; isomerisation was complete in 1 hr. for the 1-nitrosobutane dimer and in 36 hr. for the nitrosomethane dimer (*cis*-dimeric nitrosoethane and 2-methyl-1-nitrosopropane were of the same degree of stability as *cis*-dimeric nitrosomethane). Absorption maxima are given in Table 3. In each case where the pure *trans*-dimer has not been prepared, $\lambda_{max.}$ was determined for the product obtained on heating the *cis*-dimer to the m.p., cooling, re-heating to the m. p., and cooling, the process being repeated until $\lambda_{max.}$ reached a maximum. (Usually three repetitions were necessary.)

Conversion of trans-*Dimers into* cis-*Dimers.*—Ultraviolet irradiation of aqueous or ethanol solutions of pure *trans*-dimers altered the $\lambda_{max.}$ to that characteristic of the corresponding *cis*-dimer except in the case of *trans*-dimeric 2-methyl-2-nitrosopropane where $\lambda_{max.}$ was unaltered. The same behaviour was observed for solutions of the *cis*-dimer which had been heated to give a limiting $\lambda_{max.}$ value, which we claim to be that for the *trans*-dimer. Irradiation was by a Hanovia S500 lamp placed 6 in. from Unicam silica cell containing the solution, irradiation being for 1 min. Conditions were such as to give a lower limit for $\lambda_{max.}$ and only small amounts of oxime. Pyrolysis of the pure *trans*-dimers under conditions similar to those used for *trans*-dimeric nitrosomethane[4] gave coloured (yellow-brown to blue) solids in the liquid-oxygen trap. On warming to room temperature these became white solids, whose absorption spectra (in H_2O) were characteristic of the pure *cis*-dimer (Bu^t) or of the *cis*-dimer slightly contaminated with the oxime (Pr^i).

Spot Tests.—Every nitroso-dimer gave the diphenylamine–concentrated sulphuric acid test.[1]

Photolysis of Alkyl Nitrites.—Photolysis was effected in a 250-ml. transparent silica bulb which contained about 1 ml. of the nitrite. The liquid was shielded from ultraviolet light, and the vapour was irradiated by the Hanovia lamp with either an unfocused or a focused beam. In the former case, the lamp was placed 6 in. from the bulb; in the second, the focusing agent was a silica bulb containing water. Irradiation times for the unfocused beam were 10 min.,

and the product was either an oil or crystals. The bulb temperature increased slightly during the unfocused runs. Product analysis was confined to the measurement of the ultraviolet absorption spectra in ether and water. The $\lambda_{max.}$ value in ether indicates the formation of nitrosoalkanes and the $\lambda_{max.}$ value in water was regularly 1—2 mμ higher than the value for the pure

TABLE 3. *Ultraviolet absorption* (wavelengths in mμ).

Nitroso-compound	In H_2O		In EtOH		In Et_2O ‡		In CCl_4	
	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
cis-Me	265	4·00	269	4·00	286	—	291	—
trans-Me	276	4·03	282·5	4·01	286	4·01	291	4·06
cis-Et	266	4·02	272	3·94	288	3·87	292	4·00
trans-Et	277	—	285	—	288	—	292	—
cis-Pr^n	268	4·04	273	3·98	291	3·96	295	4·03
trans-Pr^n	280	—	287	—	291	—	295	—
cis-Pr^i	267	4·02	273	3·87	290	3·90	295	4·00
trans-Pr^i	280	4·01	286	3·98	290	3·95	295	4·00
cis-Bu^n	268	4·06	273	3·87	291	3·94	296	4·00
trans-Bu^n	282	—	289	—	291	—	296	—
cis-Bu^i	270	4·04	276	4·00	294	3·96	298	4·02
trans-Bu^i	285	4·01	291	3·98	294	3·96	298	4·02
cis-Bu^s	269	4·02	275	3·95	293	3·89	297	4·01
trans-Bu^s	284	—	290	—	293	—	297	—
trans-Bu^t	287	—	—	—	295 *	—	—	—
					675 *	—		
cis-C_5H_{11}	271	3·98	278 †	3·86	297	3·91	300	4·01
trans-C_5H_{11}	287	—	294	—	297	—	300	—

* 295 absorption peak decreases with time, 675 peak increases with time.

† Changes very rapidly to give $\lambda_{max.}$ 294 mμ. ‡ When the ether was pumped off from the ethereal solution of *cis*-dimer, $\lambda_{max.}$ determinations on aqueous solutions of the residue always gave values characteristic of the corresponding *trans*-dimer.

cis-dimer (except in the case of the focused photolysis of ethyl nitrite, when pure crystals of *trans*-dimeric nitrosomethane, m. p. 122°, were formed). Brief irradiation of the aqueous solution altered the $\lambda_{max.}$ value to that characteristic of the pure *cis*-dimer; subsequent heating of this solution altered it to that characteristic of the *trans*-dimer. The $\lambda_{max.}$ values obtained indicate that the same nitrosoalkane was formed in both the pyrolytic and photolytic decomposition of the alkyl nitrites investigated. (Photolysis of *iso*propyl and 1 : 2 : 2-trimethylpropyl nitrite was not attempted.) Photolysis was not further investigated as the yields of nitrosoalkane were always small, and there was always considerable production of oxime.

Production of Blue Colours in Solvents.—No dimer gave a blue colour in aqueous solution, and *trans*-dimeric 2-methyl-2-nitrosopropane was different from the other dimeric nitrosoalkanes in that it gave blue solutions in organic solvents owing to production of the monomer. Neither *trans*-dimeric 2-nitrosopropane nor *trans*-dimeric 2-methyl-1-nitrosopropane gave blue colours on dissolution in organic solvents: momentary blue colorations were observed when the solutions were heated. The *cis*-dimers, with the exception of *cis*-dimeric 2-methyl-1-nitrosopropane and nitrosomethane,[4] gave blue colours on dissolution in benzene, toluene, and ether, which colour rapidly faded leaving a colourless solution. Very faint blue colours were observed on dissolution in carbon tetrachloride. Each of these solutions became blue on heating, as did chloroform, ethanol, and acetone solutions of these *cis*-dimers. *cis*-Dimeric 2-methyl-1-nitrosopropane gave blue colours in the above solvents when the solution was heated. In every case, the blue solution faded on cooling, leaving a colourless solution.

Infrared Absorption Spectra [carried out by M. ST.C. FLETT].—The following infrared absorption bands (cm.$^{-1}$) were measured on a Grubb-Parson S4 Double Beam Spectrophotometer (w = weak, m = medium, s = strong, vs = very strong), the potassium bromide disc technique being used.

trans-Dimeric 2-methyl-1-nitrosopropane: 3004 s, 2907 m, 1475 m, 1422 m, 1395 m, 1381 m, 1357 s, 1321 s, 1302 s, 1225 vs, 1174 m, 1147 s, 1126 m, 990 w, 957 w, 940 w, 887 m, 865 w, 821 m.

cis-Dimeric 2-methyl-1-nitrosopropane: 3068 m, 2968 s, 2882 s, 1600 w, 1464 s, 1431 s, 1393 vs, 1346 s, 1302 m, 1256 s, 1215 s, 1177 m, 1151 w, 1128 w, 1098 s, 1042 s, 963 w, 951 m, 904 m, 889 w, 822 w, 780 s, 683 s.

cis-Dimeric 1-nitrosopropane: 3004 s, 2907 s, 1437 s, 1413 s, 1391 m, 1339 m, 1311 w, 1271 w, 1247 w, 1212 w, 1086 w, 1042 m, 1026 w, 905 w, 808 w.

Discussion

The pyrolytic production of nitrosoalkanes from alkyl nitrites can be generally represented by the equation:

$$R_1R_2R_3C{\cdot}O{\cdot}NO \longrightarrow R_1{\cdot}NO + R_2R_3CO$$

where R_1 is the alkyl group that contains more carbon atoms than the others (R_2 and R_3 may also be hydrogen). Such an equation accounts for our major products: it has not yet been subjected to a thorough quantitative test. If radical reactions occur, then the most plausible scheme to account for our products is

$$R_1R_2R_3C{\cdot}O{\cdot}NO \longrightarrow R_1R_2R_3C{\cdot}O\cdot + NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$R_1R_2R_3C{\cdot}O\cdot \longrightarrow R_1\cdot + R_2R_3CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$R_1\cdot + NO \longrightarrow R_1{\cdot}NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Gray [7b] has shown that reactions (1) and (2) are endothermic by about 37 and 14 kcal./mole respectively. Therefore, unless reaction (2) has a reduced frequency factor, R_1 radicals will be present in approximately the same concentration as nitric oxide. It is known [10] that the reaction (4), *viz.*,

$$R_1\cdot + R_1\cdot \longrightarrow R_1{\cdot}R_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

is faster than (3) under our reaction conditions when R_1 = Me and we have pointed out [4] that this would result in the production of about 100 moles of ethane per mole of nitrosomethane. It is probable that the ratio of the rates of reactions (3) and (4) will be similar for other alkyl radicals, and consequently unless the molecular decomposition (5):

$$R_1R_2R_3C{\cdot}O{\cdot}NO \longrightarrow R_1{\cdot}NO + R_2R_3CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

participates, these pyrolyses would be expected to yield large amounts of nitric oxide and only small quantities of nitrosoalkanes. It is possible that Steacie's [5] mechanism holds at higher pressures than ours and that nitrites can have two different activation modes. This would correspond to different energy distributions within the vibrational and rotational degrees of freedom at different pressures. If this does not occur, the close agreement between Steacie's [5] activation energy values and D(RO–NO) [7b] is fortuitous, and Gray's observation [7b] of chemiluminescence in ethyl nitrite decomposition must be ascribed to chemiluminescence of the nitrosomethane or its decomposition products. Preliminary experiments with benzyl nitrite indicated that no nitrosobenzene was formed on pyrolysis: large quantities of nitric oxide were produced, and benzaldehyde was also formed. Similarly, *cyclo*hexyl and methyl*cyclo*hexyl nitrite gave no nitroso-compound on pyrolysis, suggesting that the production of nitroso-compounds depends on the nature of the groups R_1, R_2 and R_3.

The properties of dimeric 2-methyl-2-nitrosopropane provide a test of the *cis–trans*-isomerism in dimeric nitrosoalkanes. We have already noted that the bulky *tert.*-alkyl groups would make the formation of a *cis*-dimer unlikely, if not impossible, owing to steric considerations.[4] The pyrolytic production of the monomer and its subsequent dimerisation at low temperatures give a dimer, the ultraviolet absorption spectrum in water indicating a *trans*-configuration. Irradiation of this solution produces no change in $\lambda_{max.}$, again suggesting that the *cis*-dimer cannot be formed. The *trans*-dimer dissociates in organic solvents, giving a blue solution (monomer); [11] this corresponds to a gradual decrease in the absorption in ether at 295 mμ until this absorption maximum disappears, and a continual increase in the absorption at 675 mμ, reaching a maximum when the 295 mμ peak disappears. This behaviour is independent of the method of preparation, the pyrolytic product and the product from controlled oxidation of *tert.*-butylamine [11] giving identical behaviour.

The production of the monomer on dissolution of some of the *cis*-dimers in ether can be correlated with the extinction coefficients obtained at the absorption maxima in ether. All *cis*-dimers isomerise in ether to the *trans*-dimer, *cis*-dimeric nitrosomethane and *cis*-dimeric 2-methyl-1-nitrosopropane producing no monomer. For the former, the *cis*-dimer

[10] Durham and Steacie, *J. Chem. Phys.*, 1952, **20**, 582.
[11] Bamberger and Seligman, *Chem. Ber.*, 1903, **36**, 685.

is too insoluble to allow log ε to be measured; for the latter, the log ε values are identical for the two dimers. Where monomer production occurs, isomerisation to the oxime would then be possible, leading to some loss of *trans*-dimer and a low log ε value for the *cis*-dimer. Examination of Table 3 suggests that some oxime is formed after monomer production when *cis*-dimeric 2-nitrosopropane is dissolved in ether, as the log ε value is lower than for the pure *trans*-dimer. It is probable that oxime is also produced from the other *cis*-dimers.

The *trans*- are more volatile than the corresponding *cis*-dimers, and *trans*-dimeric 2-methyl-2-nitrosopropane is very volatile. The *cis*- are more soluble in polar solvents than the *trans*-dimers; as the size of the alkyl group increases, the solubility of the *cis*-dimer in solvents of low dielectric constant increases.

Tarte's results [2] for the photolysis of alkyl nitrites differ slightly from ours, mainly for nitrites containing *n*- and *iso*-alkyl groups. The differences, which are probably due to Tarte's inadequate analytical technique for nitrosoalkanes, are summarised in Table 4.

TABLE 4. *Nitrite photolyses.*

R in RO·NO	Our product	Tarte's product	R in RO·NO	Our product	Tarte's product
Pr^n	Et·NO	No nitroso-compound	Bu^s	Et·NO	A nitroso-compound
Bu^n	Pr^n·NO	" "	CH_2Bu^i	Pr^n·NO	" "
Bu^i	Pr^i·NO	Me·NO	Bu^t	Me·NO	Me·NO
			CMe_2Et	Et·NO	A nitroso-compound

There is as yet no satisfactory explanation for the differences in the properties of *trans*-dimeric nitroso-compounds. With halogenated nitroso-compounds, either the dimer is non-existent or it readily depolymerises in organic solvents. The dimer does not exist when three halogen atoms are bonded to the α-carbon atom (*e.g.*, CF_3·NO [13]), when two halogen atoms are bonded to the α-carbon atom (*e.g.*, CH_3·CCl_2·NO [13]), or when one halogen atom is bonded to an α-carbon atom that has no hydrogen atom (*e.g.*, Me_2CBr·NO [14]). The dimers exist when one halogen is bonded to an α-C atom that carries an α-hydrogen atom [*e.g.*, $(CHMeCl·NO)_2$ [15]] or when the halogen is bonded to a β-carbon atom [*e.g.*, $(Cl·CH_2·CMe_2·NO)_2$ [13]]. Such effects are attributable to alteration of the inductive effect, which when operating to its full extent can produce repulsion between the two positively charged nitrogen atoms sufficient to overcome the N–N bonding forces. It is however difficult to apply such ideas to the case of dimers containing *tert.*-alkyl groups, all of which produce the monomer when dissolved in organic solvents, without predicting similar behaviour for dimers containing primary and secondary alkyl groups. The effect of other substituents, *e.g.*, NO_2, Ac, CH_2Ac, is also difficult to explain. Energies and entropies of activation for monomer production are needed before an adequate theory of the dissociation process can be formulated.

The infrared absorption data follow the pattern of previous measurements. The *trans*-dimer investigated has its strongest absorption at 1225 cm.$^{-1}$ and is thus similar to the *trans*-dimers previously measured,[3, 4, 13] the absorption being due to the N–O stretching. The *cis*-dimers investigated have their strongest absorption bands at 1393 and 1437 cm.$^{-1}$ which are close to the 1399 cm.$^{-1}$ band which we have tentatively identified with one of the two N–O frequencies in *cis*-dimeric nitrosomethane.[4] Further studies of the infrared absorption spectra of other *cis*-dimers are required; a detailed assignment of the spectra is therefore postponed.

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[13] Haszeldine, *J.*, 1953, 2075; Banus, *ibid.*, p. 3755.
[2] Tarte, *Bull. Soc. chim. belges*, 1954, **63**, 525.
[14] Piloty, *Ber.*, 1898, **31**, 452.
[15] Steinkopf and Jürgens, *J. prakt. Chem.*, 1911, **84**, 686.

332. *The Behaviour of Ion-exchange Resins with Mixed Solvents.*

By C. W. Davies and B. D. R. Owen.

Data are presented for the swelling of some ion-exchange resins in acetone–water and dioxan–water, and for the distribution of the solvents between the external and resin phases. The use of partition chromatography on ion-exchange columns is illustrated by some experiments with the alkali-metal cations.

In an earlier paper [1] it was reported that when aqueous acetone is in contact with an ion-exchange resin the acetone distributes itself unevenly between the two phases. The present communication describes the experiments from which this result was taken, and discusses some consequences and applications of solvent partition in ion-exchange systems.

Experimental

Materials.—Three sulphonated polystyrene resins, cross-linked with 2·25%, 5·5%, and 10% divinylbenzene, were used. They were of 60—100 mesh and had a capacity of 5·25 equivalents per kg. of dry hydrogen resin. They were cycled three times with 0·5N-sodium hydroxide followed by 0·5N-hydrochloric acid, and after complete conversion into the hydrogen form were washed to constant pH with conductivity water and air-dried. The moisture content was determined by drying over phosphorus pentoxide in vacuum at 80°. Zeo-Karb 225, used in the separation experiments, was treated in the same way. It was a sample in micro-bead form and had a capacity of 5·23 equiv. per kg. of dry hydrogen resin. The Dowex 2 was a commercial sample of 200—250 mesh. It was given a similar pretreatment and was used in the chloride form.

Acetone, of AnalaR quality, was dried over freshly ignited calcium sulphate for 48 hours and was then distilled. The distillate was stored in a dark bottle protected by a calcium chloride tube. AnalaR dioxan was refluxed with sodium and fractionally distilled. The fraction boiling at 101°/760 mm. was stored in the same way. Solutions with water were made up by weight.

Lithium chloride was prepared from lithium carbonate that had been recrystallised four times from conductivity water. The other salts were of AnalaR quality.

Equilibrium Experiments.—Approximately 2 g. of sulphonic acid resin, contained in a sintered-glass crucible, were equilibrated with about 30 ml. of acetone–water for 24 hr. in a closed apparatus. The crucible was then removed, and the resin externally dried by a gentle current of air for a period fixed by preliminary experiments as that after which the rate of loss of weight fell to a small constant value. The composition of the external solution was determined [2] by a density measurement at 25°. The resin was weighed, and then washed free from acetone with water. The acetone in the resulting solution was estimated by Tomada's iodometric method.[3] The whole method of separation and analysis was reproducible to within 0·5% when predominantly aqueous solvents were used; with solvents rich in acetone the error, attributable mainly to the surface drying technique, was ±4%.

Acetone is catalytically decomposed by strong-base resins, so in the experiments with Dowex 2 dioxan–water mixtures were chosen for study. The same equilibrating apparatus was employed, about 5 g. of Dowex 2 in the chloride form being used. The concentration of dioxan in the resulting solution was found by measuring the refractive index of the latter in an Abbé refractometer at 25° with sodium light. The concentration in the resin was obtained by difference, allowance being made for the original moisture content of the resin. Comparison with a previously determined graph enabled the concentration of dioxan to be estimated to within ±0·2%, but the overall error in the equilibrium measurements was as much as ±3% in the solutions rich in dioxan.

Separation Experiments.—20 g. of Zeo-Karb 225 micro-beads in the hydrogen form were introduced as a slurry into a Pyrex-glass tube, 1 cm. in diameter, and formed a column 100 cm. high, resting on a sintered-glass disc. The glass column was closed at the top by a ground-glass stopper through which passed a tube drawn to a fine point. To prevent disturbance of

[1] Davies and Thomas, *J.*, 1952, 1607.
[2] Int. Crit. Tables, III, 112.
[3] Tomada, *J. Soc. Chem. Ind. Japan*, 1946, **40**, 1.

the resin surface a polythene disc was used to break the fall of drops. The column was conditioned by passing through it 100 ml. of 80% acetone–water at a rate of 20 ml./hr. A solution containing up to 1 milliequiv. each of lithium, sodium, and potassium chloride in the same solvent was slowly added, and formed a pale band at the top of the column. 0·7N-Hydrochloric acid in 80% acetone–water was then run through the column at 20 ml./hr. When alkali-metal cation was detected in the eluate (flame test) 10-ml. fractions were collected and evaporated to dryness on a steam-bath. The residues were heated in an oven at 130° and then dissolved in water. Free acid was determined in this solution by titration with 0·05N-sodium hydroxide and the total chloride by titration with 0·05N-silver nitrate; the difference gave the amount of alkali-metal chloride.

Isotope Fractionation.—10 ml. of 1N-lithium chloride were applied to the top of a column of Zeo-Karb 225, 40 cm. high and 10 cm. in diameter. The lithium was displaced by 0·1N-potassium chloride in 80% acetone–water, which was run on to the column at 5 ml./hr. 10-ml. fractions were collected, and the first and last fractions were examined in a mass spectrometer.

Results and Discussion

Acetone–Water Equilibria.—In Figs. 1—3 the weights of water and acetone taken up by 1 g. of dry hydrogen resin are plotted against the molar fraction of acetone in the equilibrium solution. For all three resins the water uptake falls continuously. For the 5·5% and 10% cross-linked resins the acetone uptake rises fairly rapidly to a value that thereafter remains virtually constant. In the more lightly cross-linked resin, however, the acetone uptake shows a maximum when the molar fraction of acetone in the equilibrium solution has reached a value of approximately 0·5. Up to this point the total swelling of the resin has not been greatly affected by the presence of acetone but thereafter it falls rapidly and so does the uptake of acetone. An interesting feature of the results is that in each of the three resins the decrease in the amount of water absorbed is proportional, within experimental error, to the molar fraction in the resin phase. This is shown by the points marked by crosses in the diagrams, the same numerical scale of abscissæ now representing the molar fraction of acetone in the resin phase. Since these steep lines must eventually show a very marked change of slope, somewhat as shown by the dotted line in Fig. 1, they seem to imply that not more than about 0·34 g. of water per g. of resin, that is about 4 moles of water per equiv., are firmly held by the resin, the remainder being readily displaced by acetone.

A comparison of the Figures shows, as might be expected, that the more highly cross-linked the resin and the greater its concentration of ionising groups, the more strongly is acetone excluded from the resin phase. This is brought out more clearly in Table 1,

Table 1.

2·25% D.V.B. resin			5·5% D.V.B. resin			10% D.V.B. resin		
N	$\bar{N}$	$\bar{f}$	N	$\bar{N}$	$\bar{f}$	N	$\bar{N}$	$\bar{f}$
0·043	0·032	8·09	0·053	0·039	7·94	0·050	0·010	29·4
0·083	0·068	6·42	0·103	0·061	8·22	0·103	0·029	17·3
0·118	0·080	6·79	0·135	0·072	8·08	0·218	0·064	10·8
0·143	0·120	5·02	0·212	0·098	7·03	0·310	0·081	9·19
0·240	0·159	4·50	0·310	0·132	5·64	0·400	0·087	8·60
0·358	0·201	3·69	0·433	0·152	5·10	0·503	0·115	6·96
0·512	0·255	3·21	0·610	0·181	4·72	0·585	0·109	7·73
0·525	0·260	3·17	0·750	0·202	4·46	0·605	0·118	7·18
0·715	0·297	3·01	0·775	0·212	4·28	0·725	0·139	6·47
0·883	0·343	2·81	0·900	0·227	4·16	0·750	0·134	6·72
0·945	0·359	2·71				0·790	0·126	7·21
						0·900	0·159	5·94

which gives for the same experimental points the molar fraction of acetone in the resin phase $\bar{N}$; N, the molar fraction of acetone in the solution in equilibrium with it; and $\bar{f}$, the activity coefficient of the acetone in the resin phase. $\bar{f}$ has been calculated from Morton's vapour-pressure data [4] for acetone–water systems at 20° by means of the equation

[4] Morton, *J. Phys. Chem.*, 1929, **33**, 389.

$fN = p/p_0$, where p is the partial vapour pressure of acetone over a solution of molar fraction N and activity coefficient f, and p_0 is the vapour pressure of pure acetone; the f values were then combined with our results by the equation $\bar{f} = fN/\bar{N}$.

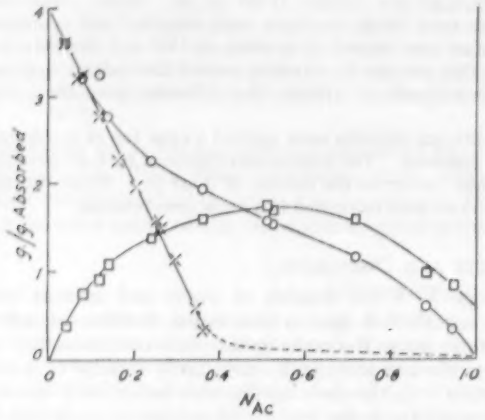
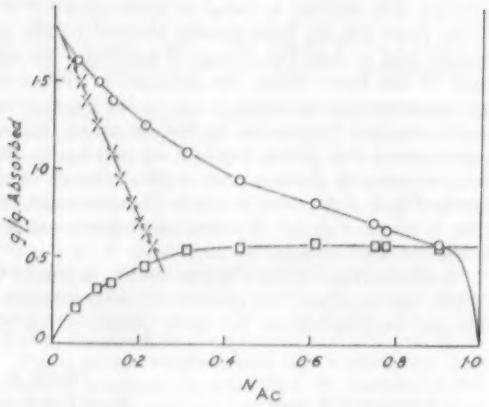


FIG. 1. 2·25% *cross-linked resin* (○ *water*; □ *acetone*).

FIG. 2. 5·5% *cross-linked resin* (○ *water*; □ *acetone*).



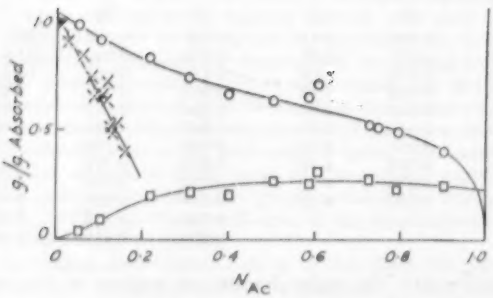


FIG. 3. 10% *cross-linked resin* (○ *water*; □ *acetone*).

Dioxan–Water Equilibria.—The results are in Fig. 4. This shows the same general features as the diagrams for the acetone–water system. The total swelling decreases only gradually until a molar fraction of 0·5 is reached in the equilibrium solution; thereafter decreasing amounts of both solvents are taken up, and the amount of swelling falls

off rapidly. The plot of water uptake against the molar fraction in the resin phase is this time perceptibly curved. The rapid change in the slope of this line must occur somewhere below 0·15 g. of water per g. of resin. The capacity of the resin was 3·8 milli-equiv./g., so this result means that not more than 2 moles of water per equiv. are strongly held by the resin in its chloride form.

Partition-Exchange Chromatography.—In ion-exchange chromatography of strong electrolytes the separation of two similar charged solutes in aqueous solution is brought about through: (1) the stronger retention of one of them by the resin, which enables the other to pass through a resin column more rapidly; or (2) the formation of unstable complexes of opposite or zero charge, which are unretarded by the resin and therefore influence, to an extent depending on their stability constants, the net rate of movement of the two

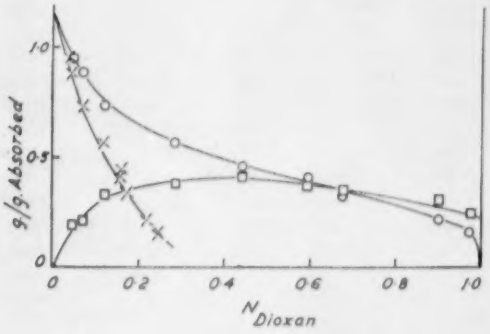


FIG. 4. *Dowex 2 resin* (○ *water*; □ *dioxan*).

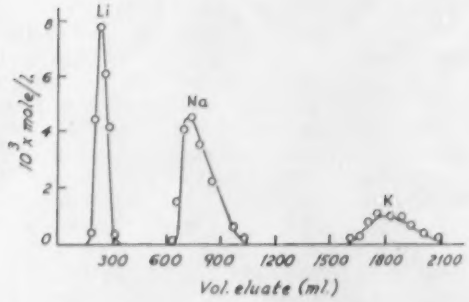


FIG. 5. *Elution curve.*

solutes down the column. The equilibrium experiments just described show that when a resin has been conditioned with a suitable mixed solvent the resin phase is predominantly aqueous and the ambient solution predominantly organic, so that conditions for partitiom chromatography between two phases of fixed composition are very conveniently set up, and the opportunity arises of using partition effects to enhance the normal separation factors.

We have illustrated the possibilities by a separation of lithium, sodium, and potassium chlorides in 80% acetone–water as solvent with 0·7N-hydrochloric acid as eluant. Beukenkamp and Rieman [5] have used aqueous 0·7N-hydrochloric acid in a successful separation of sodium and potassium ions on a column of colloidal Dowex 50, and Kayas [6] has also separated sodium, potassium, and the heavier alkali-metal ions in aqueous solution. Lithium salts are weak electrolytes in acetone, ion-pair formation increasing in the order $K^+ < Na^+ < Li^+$. It was therefore thought probable that the presence of a high concentration of acetone in the ambient solution would increase the rate of flow of lithium salts

[5] Beukenkamp and Rieman, *Analyt. Chem.*, 1950, **22**, 582.
[6] Kayas, *J. Chim. phys.*, 1950, **47**, 408.

down the column and would facilitate the separation and make the conditions for a successful separation less critical. Our elution curve is given in Fig. 5, and Table 2 shows that the separation procedure is satisfactory.

TABLE 2.

	Lithium	Sodium	Potassium
Milliequiv. introduced	0·365	0·673	0·510
Milliequiv. recovered	0·370	0·680	0·500

The volume of eluate between our sodium and potassium bands is 600 ml., and is much greater than the 140 ml. observed by Beukenkamp and Rieman when using the same concentration of eluting acid. It is likely, therefore, that a complete separation would be obtained over a wider range of conditions when 80% acetone–water is used instead of water as solvent, and that the application of the method to other difficult separations would repay study.

If the dissociation constant of ^{7}LiCl in 80% acetone–water were significantly different from that of ^{6}LiCl the method of partition-exchange would be of great value in the separation of these isotopic species. In the preliminary experiment which we carried out the ^{7}Li/^{6}Li ratios in the first and the final fractions were respectively 11·62 ± 0·03 and 11·23 ± 0·03, which are to be compared with the normal ratio of 11·52. The enrichment is significant, but not very promising. The column was short, and was not used under the conditions of maximum possible efficiency; but the result does not offer hope that the dissociation-constant difference is a very important factor in the solvent we employed.

In the ion-exchange chromatography of weak organic electrolytes in water an additional factor is introduced in the interaction of the organic solute with the resin.[7] The use of mixed solvents to modify the effect of this factor and so improve separations is illustrated in the following paper.

Absorption of Salts from Organic Solvents.—Katzin and Gebert [8] have reported that when air-dried Dowex 1 in chloride form is left in contact with acetone solutions of hydrochloric acid, or of various cobaltous, copper, lithium, or nickel salts, the resin absorbs the electrolyte almost quantitatively. For instance the copper and nickel salts are decolorised, and an originally 0·2M-solution of lithium chloride no longer gives a chloride test with silver nitrate. The authors established that the solute molecule as a whole disappeared from the liquid phase, and that the effect was influenced by the nature of the cations and anions present in the system and also by the water content of the resin. They suggest as possible mechanisms (1) that the acid is adsorbed by free weak base groups (produced by hydrolysis during washing) and (2) that the salts might be adsorbed as negatively charged complex ions. These explanations are rather difficult to accept, as there seems no other evidence for very weak basic groups in Dowex 1 or for the complex anions (especially with lithium) that have to be postulated. On the other hand, effects of the kind observed might be expected as a consequence of the distribution of solvents in the systems studied. Data are lacking for a quantitative test, but it would seem from Fig. 3 that if an air-dried resin of 20% moisture content were immersed in pure acetone, it would absorb acetone to give an inner solution with molar fraction of water of about 0·8, the outer solution remaining virtually pure acetone. Distribution coefficients of the order of 100 in favour of the aqueous phase would then explain the passage of very high percentages of a strong electrolyte from acetone solution into the resins in Katzin and Gebert's experiments.

We thank Dr. K. W. Pepper and the Director of the Chemical Research Laboratory, and also the Permutit Co. and the Dow Chemical Co. for gifts of resins used in this work; the D.S.I.R., for a maintenance award; and Dr. E. Glueckauf, who arranged for the isotopic-ratio analyses to be carried out at Harwell.

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[*Received, December 5th*, 1955.]

[7] Davies, *Biochem. J.*, 1949, **45**, 38.
[8] Katzin and Gebert, *J. Amer. Chem. Soc.*, 1953, **75**, 801.

333. *The Adsorption of Organic Acid Molecules and their Chromatographic Separation on Ion-exchange Resins.*

By C. W. Davies and B. D. R. Owen.

The molecular adsorption of some organic molecules on the strong-base resins Dowex 1 and 2 and Amberlite I.R. 410 have been measured by two indirect methods. Adsorption is even greater on these resins than on the acid exchange materials previously studied.

The interference of adsorption effects with the separation of mixtures of organic electrolytes may be entirely overcome by choice of a suitable solvent mixture. It is shown that typical mixtures of aliphatic and aromatic carboxylic acids can be quantitatively separated by ion-exchange chromatography in 35% dioxan–water as solvent.

The chromatographic separation of organic acids on ion-exchange materials has been discussed in a number of places.[1] Ideally, a series of acids may be displaced from a basic exchange resin in the order of their dissociation constants, but in practice difficulties, that have been attributed to van der Waals adsorption forces, are so great that, for example, in Partridge's work [2] on amino-acid mixtures aromatic acids had to be removed before a separation of the simpler acids was attempted.

In the present paper, adsorption data for some organic acid molecules on strong-base exchange resins are recorded, and methods are then given for removing or minimising the molecular-adsorption difficulty in the ion-exchange chromatograpy of organic materials.

Experimental

Materials.—Amberlite 410 was ground and sieved wet; the 100—120 mesh fraction was used in this work. Dowex 1 and 2 were supplied as micro-beads of 200—250 mesh. The resins were cycled three times with N-sodium hydroxide followed by N-hydrochloric acid, and the chloride forms were exhaustively washed, dried by suction, left on large filter papers for 14 days, and then stored in stoppered bottles. The moisture content of the air-dried resins was determined by heating separate samples in a vacuum oven, over phosphorus pentoxide, for 24 hr. at 80°. Columns of the resin were always kept under water and protected by soda-lime tubes. When not in actual use they were left in the chloride form.

The sodium hydroxide was standardised with AnalaR potassium hydrogen phthalate previously dried at 120°. A stream of air, free from carbon dioxide, was blown through solutions during titrations and de-ionised (carbon dioxide-free) water was used for dilutions. The acids used were AnalaR where possible.

Capacity Measurements.—The resin column was 10 cm. high and 1·2 cm. in diameter, and contained 5 g. of dry resin chloride. This was converted into the hydroxide form and washed free from alkali. A 0·1N-solution of the acid under study was then run down the column at a boundary rate of 2 cm./hr. The narrow outlet tube at the foot of the column had two small, spade-shaped, blacked platinum electrodes fused to the glass, and the resistance of the eluate was measured for each 0·5 ml. until it became constant. The fall of the resistance when acid broke through the column was not entirely sharp, but a plot of Δ (resistance) against Δ (volume) gave a symmetrical maximum which was taken to indicate the retention volume. A similar experiment in which sodium chloride was passed through the column in its chloride form enabled the "dead" volume to be estimated—the small volume of acid solution necessary to replace the solvent in the column at the beginning of each experiment. By subtracting this from the measured retention volumes, corrected values were obtained from which the total amount of each acid retained by the column could be calculated. One further small correction was necessary, as the water in the swollen resin will presumably contain organic acid molecules at virtually the same concentration as the external solution. Dowex 2 in the chloride form absorbs 1·17 g. of water/g. of resin,[3] and will therefore retain approximately 0·1 milliequiv. of

[1] See, for instance, Davies, *Biochem. J.*, 1949, **45**, 38; *Research*, 1950, **3**, 447.
[2] Partridge, *Biochem. J.*, 1949, **44**, 521.
[3] Cf. Davies and Owen, preceding paper.

acid/g. from any decinormal solution of a weak acid. A constant deduction of 0·10 milliequiv. has been made from our results, and leads to the values given in Table 1 for the amounts of acid adsorbed by 1 g. of resin in the hydroxide form.

Displacement Measurements.—A suitable quantity of acid was applied in decinormal solution to the top of a 10 cm. regenerated column of Dowex 1. Hydrochloric acid was then run on at the same rate as before. When the boundary reached the bottom of the column, samples were automatically collected, weighed, and titrated with 0·02N-sodium hydroxide in an atmosphere free from carbon dioxide. The last fractions were also analysed for chloride by subsequent titration with 0·02N-silver nitrate. Except for the first and the last fraction the concentration of the eluate was constant, and the flat portion of the concentration curve was made to extend over at least 10—15 ml. in order to fix this equilibrium concentration with accuracy. For the experiments at elevated temperatures jacketed columns were used.

Separation Experiments.—A column containing approximately 50 milliequiv. of resin was used, and for the more complex mixtures this was followed by a second, narrower, column, 6 cm. in height and 0·5 cm. in diameter. A known amount of acid mixture was applied to the top column and displaced with hydrochloric acid as in the earlier experiments. The fractions collected were titrated with sodium hydroxide solution, and the acids present were identified by submitting a drop of each fraction to paper chromatography by Hiscox and Berridge's method.[4] In overlapping fractions the amount of each acid present was estimated from the relative size of the spots. This method broke down in the separation of phenylacetic acid from benzoic acid, which have almost identical R_F values, and was supplemented by the preparation of *S*-benzylthiuronium derivatives. The melting points of these, and mixed melting points with pure derivatives, enabled the amount of overlap to be determined.

Results and Discussion

The results of our capacity measurements are given in Table 1, which shows the amounts of acid, in milliequiv., retained from 0·1N-solution by 1 g. (dry weight) of strong-base resin. Duplicate or triplicate measurements were made for each acid, and did not differ from the mean value shown by more than 0·01 milliequiv., except for phenylacetic acid where the average deviation was 0·06 milliequiv.

Table 1.

Acid	Dowex 1	Dowex 2	Amberlite 410	Acid	Dowex 1	Dowex 2	Amberlite 410
Hydrochloric...	3·45	3·84	3·26	Butyric	4·50	4·23	3·91
Formic	3·92	4·24	3·80	Valeric	—	4·88	—
Acetic	3·92	4·28	3·61	Phenylacetic...	10·4	7·3	5·5

It may be assumed that hydrochloric acid is retained wholly by salt formation, so that the hydrochloric acid value for each resin represents the exchange capacity of that resin. All the organic acids are retained in greater amounts than this, and the difference is ascribed to molecular adsorption. Figures thus derived for the molecular adsorption from 0·1N-solution are compared in Table 2 with values previously reported [5] for adsorption on acid resins.

Table 2.

Acid	Dowex 1	Dowex 2	Amberlite 410	Amberlite 100	Wofatit C
Formic	0·47	0·40	0·55	—	—
Acetic	0·47	0·44	0·35	0·16	0·14
Butyric	1·05	0·40	0·65	0·54	0·44
Phenylacetic	7·0	3·5	2·3	2·0	1·7

The present measurements were designed primarily to study the effect of molecular adsorption in column separations, and are therefore not strictly comparable with the results of the static experiments recorded in the last two columns of Table 2. Indeed, Davies and Thomas's measurements of the rate of adsorption [5] make it likely, even after allowance for the smaller particle size of the basic resins, that adsorption equilibrium had not been completely established in our present results. Nevertheless, the two series are in

[4] Hiscox and Berridge, *Nature*, 1950, **166**, 522.
[5] Davies and Thomas, *J.*, 1951, 2624.

agreement in showing both the increasing importance of molecular adsorption with rising molecular weight, and the striking effect of an aromatic constituent. Adsorption on the basic resins is always significantly greater than on the acid resins, and this can be attributed to the much greater proportion of carbon in the former. Comparisons of the results for the basic resins amongst themselves must be regarded with some caution, as the Amberlite sample was much coarser than the Dowex resins, and it is possible that adsorption on the former was therefore less complete.

TABLE 3.

			Formic acid			
Concn. of eluting acid	0·05037	0·0750	0·1001	0·1600	0·2002	0·3244
Concn. of eluate	0·0550	0·0755	0·1220	0·1980	0·2360	0·5080
			Acetic acid			
Concn. of eluting acid	0·0504	0·0750	0·1001	0·1310	0·2002	0·3244
Concn. of eluate	0·0545	0·0735	0·1160	0·1520	0·2480	0·4880
			Propionic acid			
Concn. of eluting acid	0·0504	0·1000	0·2000	0·2704		
Concn. of eluate	0·0580	0·1200	0·2960	0·4320		

Table 3 contains the results of displacement measurements. It will be seen that when a basic column, to which a little organic acid has been applied, is developed with hydrochloric acid, the displaced acid always emerges at a higher concentration than the eluting acid, and the discrepancy between the two increases with increasing concentration. This is also an effect of molecular adsorption.

The theory of displacement development for non-electrolytes on a normal adsorbent was given by Tiselius.[6] The substance, or mixture of substances, is forced down a column of adsorbent by a substance with a stronger adsorption affinity than any of the components. This " developer " displaces the other substances which in turn displace each other. If the column is uniform and sufficiently long a steady state is reached in which the components move down the column, at the same rate, in bands arranged in decreasing adsorption affinity. If a volume ΔV is introduced into the column and Δx is the distance moved by a band, $\Delta V/\Delta x_D = \Delta V/\Delta x_1 \ldots$

The movement of the front of the developer band by Δx involves a quantity of developer given by :

$$M.\Delta x.a_D + \Delta x.\alpha C_D = \Delta V.C_D$$

where M is the weight of adsorbent per unit length of column, a_D is the amount of developer adsorbed by 1 g. of adsorbent, α is the volume between the particles of adsorbent per unit length of column, and C_D is the concentration of developer. A similar equation applies to each boundary :

$$M.\Delta x.a_1 + \Delta x \,.\, \alpha C_1 = \Delta V.C_1, \text{ etc.}$$

and rearrangement of these equations gives

$$(\Delta V/\Delta x - \alpha)/M = a_D/C_D = a_1/C_1, \text{ etc.}$$

The concentration of each component therefore depends upon its specific adsorption.

This theory does not apply to acids or bases moving down exchange columns without modification. For strong electrolytes which are bound on the column by salt formation alone the adsorptive capacity of the resin is simply the exchange capacity and is the same for all, so that the effluent (whether separation is complete or not) will throughout have the same concentration as the developer solution. For a weak electrolyte in the absence of complications from molecular adsorption or hydrolysis, the same considerations will apply if a correction is made for the undissociated molecules absorbed by the swollen resin; the quantity α will retain its original meaning for the completely dissociated developer acid

[6] Tiselius, *Arkiv Kem. Min. Geol.*, 1943, *A*, **16**, No. 18.

but must be replaced by α', which allows also for the absorbed molecules, in the equations for a weak-acid boundary. This correction amounts to about 3% for 0·1N-acid of dissociation constant 1×10^{-5} and so is quite inadequate to account for the figures of Table 3, where specific adsorption effects must again be invoked to explain the high and varying eluate concentrations. Under these conditions the equation for the boundary movement of the developer may be written:

$$M\Delta x.\bar{C} + \Delta x.\alpha C_D = \Delta V.C_D, \text{ or } \bar{C}/C_D = (\Delta V/\Delta x - \alpha)/M,$$

where $\bar{C}$ is the exchange capacity per gram of the strong-base resin; but for the weak electrolytes we must write:

$$M\Delta x.\bar{C} + M.\Delta x.a_1 + \Delta x.\alpha' C_1 = \Delta V.C_1, \text{ or } (\bar{C} + a_1)/C_1 = (\Delta V/\Delta x - \alpha')/M,$$

where a_1 is the specific molecular adsorption at concentration C_1. If we neglect the small difference between α and α' we obtain:

$$(\bar{C} + a_1)/C_1 = \bar{C}/C_D, \text{ or } a_1 = (C_1/C_D - 1)\bar{C}.$$

Davies and Thomas [5] found that the Freundlich equation, $a = A \cdot C^{1/n}$, fitted their data quite well, and we have therefore plotted our values of log a_1, calculated from the equation above, against log C_1. The points show some scatter, but there is no evidence of curvature in the lines and the values found for the constants are: formic acid, $A = 3{\cdot}2$, $n = 1{\cdot}27$ ($a = 0{\cdot}54$ for $C = 0{\cdot}1$); acetic acid, $A = 3{\cdot}6$, $n = 1{\cdot}04$ ($a = 0{\cdot}39$ for $C = 0{\cdot}1$); propionic acid, $A = 3{\cdot}9$, $n = 1{\cdot}35$. As shown in parentheses, these results are in fair agreement with the estimates of adsorption made from the capacity measurements (Table 2).

Ion-exchange Chromatography of Acid Mixtures.—Molecular adsorption interferes most seriously with acid separation. We found, for instance, that formic and acetic acids can readily be separated quantitatively on Dowex 1 or Dowex 2 by displacement with hydrochloric acid; but that with a mixture of formic and phenylacetic acids the same procedure led to the displacement of the formic acid (the *stronger* acid), followed by a mixed band containing phenylacetic and hydrochloric acids. We have tested three ways of attempting to overcome this complication of adsorption.

Use of a strongly adsorbed acid as developer. Attempts were made to separate acetic and phenylacetic acids on Dowex 1 and 2 by using a 0·1N-solution of naphthalene-1-sulphonic acid as developer. This is a much stronger acid than the other two and is also likely to be strongly adsorbed by the resin. The results were disappointing; acetic acid emerged in a pure fraction, but it was followed by a mixture of the other two acids. Better results might have been obtained by using slower flow-rates and high concentrations of developer, but as these procedures would have practical disadvantages this method was abandoned.

Use of elevated temperatures. As a rise of temperature would be expected to reduce specific adsorptions, the adsorption of phenylacetic acid from 0·1N-solution was measured at a series of temperatures by the break-through capacity method. The results, in milli-equiv./g., are in Table 4.

TABLE 4.

Temp., °c	20	50	70	80	90
Dowex 1	10·4	7·2	—	5·4	5·4
Dowex 2	7·3	—	5·6	4·6	4·6

These results made it appear doubtful whether the improved separations on jacketted columns would compensate for their practical disadvantages, and attention was therefore directed to the third method.

Use of mixed solvents. Changes of solvent, as well as of temperature, may be used to modify the extent of adsorption of a substance. Break-through volumes were therefore measured on Dowex 2 for 0·1N solutions of phenylacetic acid in various dioxan–water mixtures,[3] and gave the results shown in Table 5.

Clearly adsorption is strikingly reduced in this solvent, and some typical acid separations with 0·1N-hydrochloric acid as developer were next studied, 35% dioxan (v/v) being used as solvent. Table 6 gives the results. The amounts of each acid applied to, and recovered from, the column are expressed in milliequiv. The order of elution of the acids is that given by reading down Col. 1 of Table 6.

TABLE 5. 0·1N-*Phenylacetic acid on Dowex* 2.

Dioxan, vol. %	0	10	28·9	32·5	40·0	50·0	64·4	81·5
Capacity (mequiv./g.) ...	7·34	5·40	4·38	4·06	3·76	3·75	3·77	3·76

These separations leave little to be desired. So far as can be judged by paper chromatography and the other tests applied the separations were complete, and within the possible error the amount of acid recovered was always the same as that applied. The acids appear in the theoretical order of their dissociation constants and there is a satisfactory separation in this order even of formic and phenylacetic acids, where large adsorption effects lead to a reversal of order in water. It may be noticed, too, that quite small differences in

TABLE 6.

Acid	Dissociation constant × 10^5	Applied (mequiv.)	Recovered (mequiv.)	Error, %
Butyric–phenylacetic acid separation				
Butyric	1·51	0·968	0·974	+ 0·7
Phenylacetic	4·88	0·805	0·805	—
Formic–acetic–propionic–phenylacetic acid separation				
Propionic	1·34	1·000	0·999	−0·1
Acetic	1·75	1·009	1·008	−0·1
Phenylacetic	4·88	0·804	0·804	—
Formic	17·7	1·410	1·405	−0·4
Acetic–phenylacetic–benzoic acid separation				
Acetic	1·75	0·953	0·949	−0·4
Phenylacetic	4·88	0·897	0·892	−0·5
Benzoic	6·30	1·060	1·058	−0·2

dissociation constant lead to perfect separations so long as complicating factors are eliminated.

This use of appropriate mixed solvents seems likely to be of very general value in the separation of organic mixtures. The beneficial effect of the organic solvent is primarily in the reduction in the amount of solute adsorbed, but will also be exerted in increasing the rate of attainment of adsorption equilibrium, since the exchange of an organic solvent molecule for a solute molecule at an adsorption site will involve a much smaller energy increment than will the desorption of the solute molecule in water. The partition effect will also normally lead to improved separations; in the experiments recorded in Table 6 the effluent concentrations were appreciably greater than decinormal, from which it may be deduced that the partition of the acids between the predominantly aqueous resin phase and the external phase was markedly in favour of the latter.

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334. *A Study of the Stephen Reaction.*

By L. Turner.

A modified form of the Stephen reagent has been used in comparing the rates of reduction of a number of unsubstituted aliphatic and substituted aromatic nitriles. The reaction is of neither the first nor the second order. Precipitation of the aldiminium stannichloride appears to be the main factor which drives the reaction to completion. In unsubstituted aliphatic nitriles, structure has little effect on the rate of reaction, whereas in substituted benzonitriles electron-repelling groups increase the rate appreciably.

The scope of the reaction in the aliphatic series has been clarified by measuring the yields of aldehyde from the simpler nitriles. The yield increases with chain-length, but is lowered by chain-branching in the α-position.

Attention is drawn to the usefulness of the nitrile-exchange reaction [1] in the synthesis of *iso*butyro- and pivalo-nitrile.

The Stephen reaction,[2] in which nitriles are reduced to aldimines (subsequently hydrolysed to aldehydes) by ethereal stannous chloride and hydrogen chloride, has recently been reviewed,[3, 4, 5] whence it is clear that the scope of the reaction in the aliphatic series is in doubt, and that there is little or no evidence concerning its mechanism. The present work consists of exploratory studies of the kinetics of the reaction, and of the determination of the yields of aldehydes from the lower aliphatic nitriles.

The reagent, as normally prepared,[2] is not suitable for kinetic studies, since it consists of two immiscible layers. A homogeneous reagent may be conveniently prepared by adding acetyl chloride to stannous chloride dihydrate in ether, the anhydrous salt being produced, together with some of the hydrogen chloride required for the reaction. Extra hydrogen chloride may be added by running in acetyl chloride and water in equimolar amounts. The acetic acid so produced renders the mixture homogeneous, and the reagent is stable for some weeks in a stoppered flask.

The course of the reaction has been followed by periodical determination of the stannous chloride concentration by standard, aqueous iodine. During the reaction the aldimine, which is the final product of the reduction, is precipitated as stannichloride. Fortunately, when the modified reagent was used, this precipitation was delayed, and measurements could be made under homogeneous conditions over the first 10—20% of the reaction.

The effects of varying the concentration of nitrile, of stannous chloride, and of hydrogen chloride are shown, for benzonitrile, in Tables 1—3. The rate varied with the concentration

Table 1. *Variation of rate with concentration of benzonitrile.*

Temp.: 23·6° ± 0·1°. Solvent: 30% v/v acetic acid in ether.
$[SnCl_2]$ = 0·471M. [HCl] = 0·444M.

Time (hr.):	2	5	10	20	50
Concn. of nitrile (M)	$SnCl_2$ (10^{-3} mole) consumed				
0·551	0·91	1·95	2·82	3·25	3·35
0·184	0·16	0·36	0·65	1·12	1·84
0·055	0·08	0·16	0·26	0·38	0·49

of each, and, as would be expected, the usual calculations showed that the reaction was kinetically neither of the first nor of the second order. An increase in the concentration of either the nitrile or hydrogen chloride increased the rate. The same was true for stannous chloride, except that there was an inversion of two of the concentration-time curves

[1] B.P. 722,843.
[2] Stephen, *J.*, 1925, 1874.
[3] Wagner and Zook, "Synthetic Organic Chemistry," J. Wiley and Sons, New York, 1953, p. 292.
[4] Mosettig, "Organic Reactions," J. Wiley and Sons, New York, 1954, Vol. VIII, p. 246.
[5] Bayer, "Methoden der organischen Chemie (Houben–Weyl)," G. Thieme, Stuttgart, 4th Edn., Vol. VII, Pt. 1.

TABLE 2. *Variation of rate with concentration of stannous chloride.*

Temp. and solvent as in Table 1. [Ph·CN] = 0·551M. [HCl] = 0·767M.

Time (hr.):	1	2·5	5	10	25
Concn. of $SnCl_2$ (M)	$SnCl_2$ (10^{-3} mole) consumed				
0·384	1·38	2·54	3·27	4·02	4·93
0·145	2·02	2·54	2·97	3·38	3·87
0·055	0·98	1·28	1·38	1·48	1·62

TABLE 3. *Variation of rate with concentration of hydrogen chloride.*

Temp. and solvent as Table 1. [Ph·CN] = 0·551M. [$SnCl_2$] = 0·325M.

Time (hr.):	1	2·5	5	10	20
Concn. of HCl (M)	$SnCl_2$ (10^{-3} mole) consumed				
3·47	0·91	1·65	2·45	3·54	5·50
2·14	0·27	0·58	0·98	1·50	2·16
0·98	0·08	0·19	0·34	0·51	0·62

in the early stages of the reaction. These results are in conformity with a mechanism proposed for the reaction by Meerwein,[6] the first step in which may be interpreted as the formation of the nitrilium salt from the nitrile and chlorostannous acid:

$$R{\cdot}CN + H_2SnCl_4 \longrightarrow [R{\cdot}C{\equiv}NH]^+HSnCl_4^-$$

Since the concentration of chlorostannous acid must depend on the concentration of both stannous chloride and hydrogen chloride, the rate of reaction should vary with the concentration of all three reactants, as is found.

Attention was next turned to the effect of the structure of the nitrile on the reaction rate. The reaction being of indeterminate order, no quantitative comparison of rate-constants was possible. It was also impossible to take the initial slope of a concentration–time curve as a measure of rate since the necessary pipetting of the 1 ml. aliquot parts of ethereal solution involved an error estimated to be about 1·5—2%, which was significant in the very early stages of the reaction. However, reasonably smooth concentration–time curves were obtained, covering an adequate portion of the reaction, and the rates for various nitriles could be compared qualitatively.

For aliphatic nitriles the reagent used contained four mols. of hydrogen chloride per mol. of stannous chloride, the reaction being inconveniently slow at smaller concentrations. The results (Table 4) show that the structure has only a minor effect on the *rate* of reaction

TABLE 4. *Variation of rate with structure: aliphatic nitriles.*

Temp. and solvent as Table 1. [R·CN] = 0·540M. [$SnCl_2$] = 0·372M. [HCl] = 1·49M.

	Time (hr.):	2	5	10	25	50
$SnCl_2$ (10^{-3} mole) consumed	MeCN	0·65	0·97	1·32	2·00 *	4·26
	EtCN	0·36	0·84	1·28	1·78	2·25
	Pr^{n}CN	0·48	0·90	1·18	1·49	1·74
	Pr^{i}CN	0·32	0·65	1·07	1·56	1·84
	Bu^{t}CN	0·69	1·45	2·18	2·74	2·90

* Precipitation of the aldimine stannichloride set in after about 25 hr.

of aliphatic nitriles (the effect on the yield is later shown to be more marked). With acetonitrile, precipitation of the aldimine stannichloride occurred after 25 hr., and markedly accelerated the reaction. Such precipitation is thus a major factor in driving the reaction to completion, *i.e.*, in producing high yields (this was confirmed in the experiments with aromatic nitriles). It would also serve to remove the aldimine salt from the reaction zone, thus hindering the formation of the by-product isolated by Knight and Zook [7] in work with lauronitrile, *viz.*, the *NN'*-alkylidenebisacylamide $CHR(NH{\cdot}COR)_2$.

[6] Meerwein, personal communication to Bayer in ref. 5.
[7] Knight and Zook, *J. Amer. Chem. Soc.*, 1952, **74**, 4561.

The rates of reduction of benzonitrile, *o*- and *p*-tolunitrile, *o*- and *p*-chlorobenzonitrile, and α-naphthonitrile were next compared, reagent containing only two mols. of hydrogen chloride per mol. of stannous chloride being used since at higher concentrations early precipitation of the aldimine salt occurred, restricting the measurements to only a small proportion of the total reaction. The results are shown in Table 5. *o*- or *p*-Methyl or -chloro-groups in benzonitrile markedly increase the reaction rate. The acceleration caused by the precipitation of the aldimine salt was again pronounced in the experiment with *p*-chlorobenzonitrile (with benzonitrile, *p*-tolunitrile, and *o*-chlorobenzonitrile, precipitation accompanied by acceleration occurred at a later stage, not shown in the Table).

TABLE 5. *Variation of rate with structure: aromatic nitriles.*

Temp.: 23·6°/± 0·1°. Solvent: 41% (v/v) acetic acid in ether.
[R·CN] = 0·540M. [$SnCl_4$] = 0·300M. [HCl] = 0·600M.

	Time (hr.):	1	2	5	10	25
$SnCl_4$ (10^{-3} mole) consumed	Ph·CN	0·29	0·36	0·60	0·87	1·66
	o-Cl·C_6H_4·CN	0·55	0·87	1·30	1·74	2·45
	p-Cl·C_6H_4·CN	1·13	1·74	2·26	2·44 *	4·66
	o-Me·C_6H_4·CN	1·20	1·48	1·71	1·81	2·10
	p-Me·C_6H_4·CN	0·62	0·88	1·26	1·52	1·77
	α-$C_{10}H_7$·CN	0	0	0	0	0·57

* Precipitation of the aldimine stannichloride set in after about 12 hr.

o-Tolunitrile and α-naphthonitrile both give low yields of aldehyde in the Stephen reaction,[4] although some reduction to the aldimine occurs, as shown by the above results. Rather surprisingly, *o*-tolunitrile was found to be reduced faster than was benzonitrile, in the early stages, after which period the reaction virtually stopped, probably because of the failure of the *o*-tolualdiminium stannichloride to be precipitated and so drive the reaction forward. During the earlier work, it had been noticed that the precipitation of the aldimine salt was favoured by low stannous chloride and high hydrogen chloride concentration, but under these conditions neither nitrile gave the desired precipitate, even after some weeks.

The scope of the reaction in the aliphatic series has been clarified by determining the yields of aldehyde from aceto-, propio-, *n*-butyro-, *n*-valero-, *iso*butyro-, and pivalo-nitrile. The modified reagent, as initially prepared, contained two mols. of hydrogen chloride per mol. of stannous chloride, and was saturated with hydrogen chloride before use. The exact concentration of hydrogen chloride was not determined.

Lieber [8] has claimed that, under certain conditions, the aldimine from lauronitrile was not precipitated as its stannichloride but remained in solution. In these experiments, therefore, both the precipitated salt and the mother-liquor were worked up for aldehyde, which was indeed produced from both sources on hydrolysis. The yield of aldehyde was determined quantitatively by the bisulphite method of Bell and Brown.[9] Control analyses of samples of the pure aldehydes enabled corrections to be made for losses during hydrolysis. The results are summarised in Table 6. The figures quoted in footnote (*b*) show that the modified reagent gives yields of aldehyde comparable with those obtained by the normal procedure. The reaction was much slower in the former case, and the modified reagent has little to recommend it in preparative work.

The lower aliphatic nitriles give only poor to moderate yields in the Stephen reaction, the yield from normal nitriles increasing with chain length. Chain-branching in the α-position lowers the yield (this may be confirmed from Table 6 in Mosettig's review [4]).

Knight and Zook [7] have cast some doubt on the constitution of the precipitate obtained by Lieber [8] from lauronitrile, implying that it might not have been the aldiminium stannichloride. Analyses of the precipitates isolated during this work showed that they were probably somewhat impure samples of the expected aldimine salt. They yielded about 90% of the theoretical amount of aldehyde on hydrolysis, and contained about 90% of the theoretical content of tin.

[8] Lieber, *ibid.*, 1949, **71**, 2862.
[9] Bell and Brown, *J.*, 1954, 774.

Attention is drawn here to the extremely useful " nitrile-exchange " reaction,[1] details of which have recently been published as a Patent. When a carboxylic acid is boiled with phenylacetonitrile, in the presence of a strong acid catalyst, *e.g.*, sulphuric acid or a sulphonic acid, an exchange occurs, and the nitrile corresponding to the acid may be removed

TABLE 6. *Yields (%) of aldehydes from the lower aliphatic nitriles.*

Nitrile	Yield of aldehyde from precipitate	Yield of aldehyde from mother-liquor	Aldehyde semicarbazone [a] m. p.	Aldehyde semicarbazone [a] lit.	Nitrile	Yield of aldehyde from precipitate	Yield of aldehyde from mother-liquor	Aldehyde semicarbazone [a] m. p.	Aldehyde semicarbazone [a] lit.
MeCN ...	25 [b]	5	—	—	Bu^nCN...	44 [b]	17	103—104°	[c]
EtCN ...	15	8	88°	89°	Pr^iCN ...	13	12	125	126°
Pr^nCN ...	40	13	104	106	Bu^iCN...	10	12	189	190

[a] Semicarbazones were recrystallised from ethanol–water. [b] When Stephen's original procedure [2] was followed, aceto- and *n*-valero-nitrile gave, respectively, 32% and 42% yields of aldehyde from the aldiminium stannichloride only. [c] New compound. An authentic specimen of *n*-valeraldehyde semicarbazone had m. p. 104° (Found: N, 29·1. $C_6H_{13}ON_3$ requires N, 29·4%).

by fractional distillation, provided that its boiling point is lower than that of any other component. The direct preparation of *iso*butyro- and pivalo-nitrile from the corresponding acids is now reported, the yields being 49 and 56% respectively.

EXPERIMENTAL

Sodium-dried ether, freshly-distilled acetyl chloride, and commercial stannous chloride dihydrate were used to prepare the reagent. Anhydrous stannous chloride was made by the method recommended by Stephen.[10]

Commercial samples of normal aliphatic nitriles and liquid aromatic nitriles were treated with concentrated hydrochloric acid until the smell of *iso*nitrile had gone, dried (K_2CO_3) and fractionated through a 6" Vigreux column. *iso*Butyro- and pivalo-nitrile were made by nitrile exchange between the corresponding acids and phenylacetonitrile. Solid aromatic nitriles were recrystallised from benzene–light petroleum (b. p. 40—60°), until of constant m. p. *o*-Chlorobenzonitrile had m. p. 45—46° (lit., 42°).

Preparation of the Modified Reagent.—A typical mixture was made as follows. Stannous chloride dihydrate (112·8 g., 0·5 mole) was suspended in ether (133 ml.), in a flask sealed by a U-tube containing a little mercury. Acetyl chloride (71 ml., 1·0 mole) was added at a such rate that no hydrogen chloride escaped past the mercury seal (slight cooling was necessary). The homogeneous liquid so produced contained 30% and 70% respectively of acetic acid and ether, by volume. It was diluted to 500 ml. by the addition of a mixture of acetic acid and ether in the same proportions (called below " mixed solvent ").

Effect of Nitrile Concentration on Rate.—Into each of three stoppered flasks containing the reagent (25 ml.) diluted with mixed solvent (to 50 ml.) were pipetted, respectively, 3 ml. (0·0292 mole), 1 ml. (0·00973 mole), and 0·3 ml.(0·00292 mole) of benzonitrile. The volume of each solution was raised to 53 ml. by the addition of mixed solvent. All solutions were brought to the thermostat temperature (23·6° ± 0·1° throughout all kinetic measurements) before mixing. Aliquot parts (1·00 ml.) were withdrawn at approximately zero, 1, 3, 8, 24, and 50 hr., and were run into N-hydrochloric acid (10 ml.). Stannous ion was then determined by titration (starch) against aqueous iodine (0·05M). The fall in stannous chloride concentration was calculated from the titration differences.

Effect of Stannous Chloride Concentration on Rate.—(*a*) Reagent solution containing 0·384 mole/l. of stannous chloride was made by diluting 25 ml. of a stock solution to 50 ml., with mixed solvent. Benzonitrile (3 ml., 0·0292 mole) was added. The hydrogen chloride concentration was 0·767 mol./l.

(*b*) Reagent solution containing 0·145 mole/l. of stannous chloride was made as follows. To the stock solution (10 ml.) were added acetyl chloride (2·13 ml., 0·03 mole) and water (0·54 ml., 0·03 mol.), which generated the hydrogen chloride sufficient to maintain the final concentration at 0·767 mole/l. Ether (4·0 ml.) was added to compensate for the acetic acid produced by the previous operation, and the whole was made up to 50 ml. with mixed solvent. Benzonitrile was added as before.

[10] Stephen, *J.*, 1930, 2786.

(*c*) Reagent containing 0·0554 mole/l. of stannous chloride was made as in the previous paragraph, from stock solution (5 ml.), acetyl chloride (2·84 ml., 0·04 mole), water (0·72 ml., 0·04 mole), ether (5·33 ml.), and mixed solvent up to 50 ml. Benzonitrile was added as before. The concentration–time curve was constructed from measurements taken as in the preceding section.

Effect of Hydrogen Chloride Concentration on the Rate of Reaction.—To a known volume of the stock reagent, extra hydrogen chloride was added by running in equimolar amounts of acetyl chloride and water. The calculated amount of ether was added to restore the composition of the solvent to its standard value, and the mixture was diluted by mixed solvent to a fixed volume. The stock solution used contained 0·69 mole/l. of stannous chloride and 2·07 mole/l. of hydrogen chloride. Three experiments were carried out with the following quantities respectively: (*a*) Stock solution (25 ml.); mixed solvent up to 50 ml.; benzonitrile (3 ml.). (*b*) Stock solution (25 ml.), acetyl chloride (4·66 ml., 0·061 mole), water (1·19 ml., 0·061 mole), ether (8·8 ml.), and mixed solvent up to 50 ml. (*c*) Stock solution (25 ml.), acetyl chloride (9·32 ml., 0·132 mole), water (2·37 ml., 0·132 mole), ether (17·6 ml.), and mixed solvent up to 50 ml.

Effect of Nitrile Structure on the Rate of Reaction.—(*a*) *Aliphatic nitriles.* To a stock solution of reagent (25 ml., containing 0·788 mole/l. of stannous chloride and 3·152 mole/l. of hydrogen chloride) were added the nitrile (0·0286 mole) and mixed solvent (up to 53 ml.). The measurements of rate were made as before.

(*b*) *Aromatic nitriles.* Measurements were made as for the aliphatic nitriles, a stock reagent solution containing stannous chloride (0·752 mole/l.) and hydrogen chloride (1·504 mole/l.) being used. At this lower hydrogen chloride concentration slight precipitation of white crystals occurred when the stock solution was diluted with the mixed solvent, and the final mixture was diluted to 63 ml. by the addition of acetic acid, which caused the crystals to redissolve.

Attempted Reaction of o-Tolunitrile and α-Naphthonitrile under Forcing Conditions.—To the stock reagent solution (5 ml., as used for aromatic nitriles, see previous paragraph) were added acetyl chloride (6·4 ml.), water (1·62 ml.), ether (15·9 ml.), and mixed solvent (up to 50 ml.). The nitrile (0·02 mole) was added, and the volume made up to 53 ml. with mixed solvent. The product contained 0·072, 1·834, and 0·377 mole/l. respectively of stannous chloride, hydrogen chloride, and nitrile. No precipitate was formed after two weeks at 20° and a further week at 0°.

Determination of the Yields of Aldehyde from Aliphatic Nitriles.—To a stirred suspension of stannous chloride dihydrate (16·8 g., 0·075 mole) in ether (50 ml.) was added an excess of acetyl chloride (13·0 ml., 0·195 mole). The mixture was saturated with dry hydrogen chloride, and to the homogeneous product the nitrile (0·05 mole) was added. After 7 days the precipitated aldiminium stannichloride was filtered off, washed with ether, and dried at 50°/20 mm. The combined filtrate and washings were retained for analysis.

The amount of aldehyde obtainable by hydrolysis of the precipitate was determined as follows. A weighed amount (*ca.* 0·7 g.) of the salt was boiled with N-hydrochloric acid (55 ml.), and about 20 ml. of the distillate were collected in an excess of aqueous sodium hydrogen sulphite (50 ml.; 0·5M), contained in three wash-bottles in series. The sulphite solution was made up to 100 ml. with water, and the excess sulphite in a 5 ml. sample destroyed by titration with 0·5M- and finally 0·03M-iodine. An excess of solid sodium hydrogen carbonate was added, and the liberated sulphite titrated against 0·03M-iodine. The percentage of aldehyde obtained from the salt was then calculated, and the value multiplied by the "recovery factor" of the aldehyde (see next paragraph).

The amount of aldehyde obtainable from the mother-liquor was determined by distilling off the solvent, drying the residue at 70°/20 mm., hydrolysing the product with N-hydrochloric acid (50 ml.), and determining the aldehyde produced as before.

Determination of Aldehyde "Recovery Factors."—A weighed quantity (*ca.* 0·005 mole) of freshly distilled aldehyde was added to a solution of stannic chloride (1 ml.) in N-hydrochloric acid (50 ml.). The mixture was distilled, and the aldehyde in the distillate estimated as above. The "recovery factor" was expressed as (wt. of aldehyde taken)/(wt. recovered). The factors were all about 1·1, except that of pivalaldehyde, which was 1·72.

Determination of the Tin Content of Aldiminium Stannichlorides.—The liquid remaining in the flask after hydrolysis of the salt and removal of aldehyde (see above) contained all the tin, as chloride. Water (to 100 ml.), and then concentrated hydrochloric acid (40 ml.) were added, and the liquid was boiled with a spiral of nickel foil for 1 hr., in a flask sealed by an outlet tube dipping into aqueous sodium hydrogen carbonate. A few marble chips were then added, to

give an inert atmosphere of carbon dioxide, the nickel was removed and washed, and the stannous tin in the cooled solution titrated against aqueous iodine (0·03M) (starch). The tin content was in all cases about 90% of that calculated for $[R{\cdot}CH{:}NH_2^+]_2SnCl_6^{2-}$, except when R was Me, in which case values were consistently high.

Preparation of iso*Butyro- and Pivalo-nitrile.*—The appropriate carboxylic acid (1 mol.), phenylacetonitrile (3 mols.), and concentrated sulphuric acid (0·01 mol.) were boiled under reflux for 30 min. The nitrile was then slowly distilled off, through a 6-inch Vigreux column, and freed from traces of acid by a further fractional distillation from about one-tenth of its volume of *o*-toluidine. *iso*Butyronitrile (b. p. 103—104°) was obtained in 40% yield, and pivalonitrile (b. p. 104—105°) in 56% yield.

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335. *Mechanism, Kinetics, and Stereochemistry of Octahedral Substitutions. Part IV.* Bimolecular Basic Hydrolysis and Aquation of Some Halogeno*iso*thiocyanatobis(ethylenediamine)cobalt*(III) *Ions.*

By C. K. Ingold, R. S. Nyholm, and M. L. Tobe.

This paper reports the beginning of an investigation of the steric course in kinetically controlled conditions of bimolecular nucleophilic substitutions at octahedral cobalt. In the present group of experiments an attacking hydroxide ion in solvent water displaces halogen from a halogeno*iso*thiocyanatobis(ethylenediamine)cobalt(III) ion. The reactions are bimolecular, not only overall, but also with respect to the formation of each of the stereoisomeric products, which thus appear in constant ratios. The products suffer no reversible interconversion in the conditions of their formation, although at late times a further stage of substitution sets in with displacement of the *iso*thiocyanato-group. At 0°, the *trans*-chloro-cation gives 76%, the *trans*-bromo-cation 81%, and the *cis*-chloro-cation 82% of *cis*-isomer in the mixture of *cis*- and *trans*-hydroxy-cations formed. Thus stereo-change in bimolecular nucleophilic substitution at octahedral cobalt is not exclusive, as it is at tetrahedral carbon.

Rates of aquation in dilute aqueous acid of the *trans*-chloro- and *trans*-bromo-cations have been measured. The products formed are here to be distinguished from the products found, because the *cis*- and *trans*-aquo-isomers undergo reversible interconversion in the conditions of their formation. Because of this complication the stereochemistry of the aquation of the chloro-cation could not be adequately determined, but the aquation products formed from the bromo-cation were shown by a kinetic analysis to contain 43—46% of the *cis*-aquo-isomer at 63—90°. It is thus clear that aquation can pursue a course involving stereo-change.

The rates of interconversion of the *cis*- and *trans*-aquo-isomers have been measured. At 63—90°, some 81—84% of the *cis*-isomer is present at equilibrium.

In Parts I and II * it was shown that the two mechanisms, S_N1 and S_N2, of nucleophilic substitution, which have long been familiar in organic chemistry, both participate in the ligand substitutions of octahedrally co-ordinated atoms, in particular of cobalt(III). In Part II kinetic criteria for the recognition of these mechanisms were developed. These results prepared the way for an investigation of the spatial orientation of octahedral substitution, under each of the two mechanisms, by a combined study of products and kinetics. In Part III,* this investigation was commenced on the side of the unimolecular

* Part I, *J.*, 1953, 2674; Part II, *ibid.*, p. 2680; Part III, *ibid.*, p. 2696.

mechanism of substitution, S_N1, using a cobalt(III) octahedral centre; and now, the more fully to launch our programme, we report in these papers our first results on spatial orientation in the bimolecular mechanisms of substitution, S_N2, again at octahedral cobalt(III).

We have studied bimolecular substitution in bis(ethylenediamine)cobalt(III) complexes containing one displaced group, and one characteristic non-replaced group, both groups being treated as variable features of the structure. Up to the present, our displaced groups have been the chloro-, bromo-, and nitrato-ligands. As characteristic retained groups, we now report on the *iso*thiocyanato- and ammino-ligands. The other possible constitutional variable, the introduced group, has not yet been made to vary, inasmuch as the work to be reported is concerned only with hydroxide ion as substituting agent, in solvent water. Water itself is highly active in cobalt substitutions: we know that it cannot be used as solvent in the study of unimolecular substitutions by weakly nucleophilic substituting agents, because it then usurps the functions of substituting agent: and the price one pays for the convenience of using water in the study of bimolecular substitutions is that one is practically limited to the hydroxide ion as reagent, since this is the only stable anion that is sufficiently highly nucleophilic to attack the cobalt atom much faster than the water can, thereby securing that the substitution proceeds directly, and does not go, as many substitutions by anions in aqueous solutions do go, through the route of a preliminary aquation.

Most of the earlier literature of kinetic and stereochemical studies of octahedral substitutions is cited in Part I. In none of this work are the two methods of investigation so combined that an observed stereochemical outcome of substitution can be related to an established mechanism. Some further stereochemical results for cobalt(III) substitutions have since become available,[1] but they too are unassociated with kinetic evidence of mechanism. Parts II and III of this series described an integrated kinetic and stereochemical study of substitutions in the cobalt(III) complex, but only for unimolecular substitutions S_N1.

In the present paper we report a combined kinetic and stereochemical examination of three substitutions in the cobalt(III) system, all proceeding by the bimolecular mechanism S_N2. In each, the hydroxide ion, attacking in aqueous solution, displaces a halogen as halide ion from a bis(ethylenediamine)cobalt(III) ion containing a retained *iso*thiocyanato-ligand. We also report a kinetic and stereochemical study of the aquations of the same complex ions, and a kinetic study of a reversible isomerisation of their stereoisomeric aquo-derivatives.

(I) *Kinetics and Products of the Reactions of Hydroxide Ion with* trans-*Chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *Ion in Water:*

$$OH^- + \textit{trans}\text{-}[Co\ en_2(NCS)Cl]^+ \longrightarrow \textit{cis}\text{- and }\textit{trans}\text{-}[Co\ en_2(NCS)OH]^+ + Cl^-$$

(1.1) *Basic Chemistry.*—The *cis*- and *trans*-series of salts of chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) are both well characterised. Their stereochemistry is made certain by the optical resolution of salts of the *cis*-series; and equally by the conversion of the *trans*-salts, without rupture of the cobalt–nitrogen bond, into *trans*-salts of the chloroamminobis(ethylenediamine) series, which are known as to configuration, because the isomeric *cis*-chloroammino-salts have been resolved.[2]

When a dilute aqueous solution of a *trans*-salt, such as the bromide, perchlorate, thiocyanate, or dithionate, is treated with dilute sodium hydroxide, the colour changes slowly from purple to orange-pink. This is a visible sign of the reaction formulated above. This reaction can at any stage be stopped by the addition of acid, which also instantaneously protonates the formed *cis*- and *trans*-hydroxy*iso*thiocyanato-cations to give the *cis*- and *trans*-aquo*iso*thiocyanatobis(ethylenediamine)cobalt(III) ions; and it is by way of these protonated derivatives that the immediate products of the substitution have been examined.

[1] Basolo, Stone, and Pearson, *J. Amer. Chem. Soc.*, 1953, **75**, 819.

[2] (*a*) Werner, *Annalen*, 1912, **386**, 1; (*b*) Tupizina, Diss., Zürich, 1915; (*c*) Mathieu, *Bull. Soc. chim. France*, 1936, **3**, 484.

It is necessary to have some knowledge of the stabilities of the substances involved under the alkaline and acidic conditions employed. At the temperatures used in the study of the hydroxylation process, 0—20°, and in solutions of an acidity at least of pH 5, the *trans*-chloro-cation and the *cis*- and *trans*-aquo-cations are all stable for periods much longer than those of our hydroxylation experiments. This was established by spectrophotometric examination of solutions of pure salts of these cations prepared as described in Section (8). However, changes occur at higher temperatures, such as 50—90°, in the acidic aqueous solutions. The *trans*-chloro-cation then undergoes direct aquation, at a rate which we have measured, to give aquo*iso*thiocyanato-cations; and the *cis*- and *trans*-aquo-cations themselves undergo reversible isomerisation, the rate of which we have likewise measured. We have also measured the equilibrium attained in this balanced reaction. These and similar measurements are described in Sections (4)—(6) of this paper.

The actual process of acidification, with protonation of the *cis*- and *trans*-hydroxy-cations to give their conjugate acids, the corresponding aquo-cations, induces no stereoisomeric change. This was shown by spectrophotometric examination of solutions of pure *cis*- and *trans*-aquo-salts after repeated alternate basifications and acidifications.

In dilute alkaline solution, at the temperatures used for the displacement of chlorine by hydroxide ion from the *trans*-chloro*iso*thiocyanato-cation, the *cis*- and *trans*-hydroxy*iso*thiocyanato-cations, show no signs of isomerisation. This conclusion followed from a spectrophotometric examination of basified and kept solutions of *cis*- and *trans*-aquo*iso*thiocyanato-salts. However, the two hydroxy*iso*thiocyanato-cations were found to undergo, in these conditions, a relatively slow second stage of hydroxylation, involving displacement of the *iso*thiocyanato-group, and the formation of dihydroxybis(ethylenediamine)cobalt(III) cations. Such displacements of the *iso*thiocyanato-group were, however, slow enough not to be more than slightly troublesome in our study of the displacement of chlorine by the attack of hydroxide ion.

The *cis*- and *trans*-series of salts of aquo*iso*thiocyanatobis(ethylenediamine)cobalt(III) are themselves quite well characterised, and the isomeric cations have distinctive spectra. The assignment to them of their respective stereochemical structures was originally made by Werner on slightly dubious grounds, but correctly, as was established by the subsequent work of Mathieu.[2c,3b] From the optically active *cis*-chloro*iso*thiocyanato-cation, he obtained, by a direct and completed aquation, an optically active solution of an aquo*iso*thiocyanato-cation; and this agreed in its spectrum with the *cis*-aquo-cation to within the toleration demanded by its partial isomerisation, of which we now report the rate and equilibrium.

A number of the reactions which we have studied kinetically are appreciably accelerated by light. We, therefore, ran all rate processes in darkened vessels.

(1.2) *Kinetics.*—The rate of the alkaline hydroxylation of the *trans*-chloro*iso*thiocyanato-cation has been measured titrimetrically in aqueous methyl alcohol, and in water, at 0°, and spectrophotometrically in water only at 0°, 10°, and 20°.

The obvious titrimetric method of following liberated chloride ion with the aid of a silver electrode was unavailable, since, as Mathieu originally noted,[3b] silver ions combine with complex cobalt ions containing the *iso*thiocyanato-group. However, the aquo-*iso*thiocyanato-cations, which the formed hydroxy*iso*thiocyanato-cations produce on acidification of the reaction samples, are weak acids, and, after neutralisation of any excess of strong acid, can be titrated as such. Thus, the titration curve, as obtained by the use of a glass hydrogen electrode, shows two equivalence points, the separation of which measures the concentration of aquo-cations. The method tends to give somewhat high reaction rates, because any temporary local alkalinity during titration leads to some further hydroxylation of still undecomposed chloro-cation, and thus to high estimates of the amount of reaction at the time of sampling.

It was not possible to secure a good analytical measurement for the completed displacement of chlorine, because of the incursion at late times of the second step of hydroxylation, with displacement of the *iso*thiocyanato-group. Infinite-time values were therefore

[3] (*a*) Werner, *Arch. Sci. phys. nat. Genève*, 1911, **32**, 457; (*b*) Mathieu, *Bull. Soc. chim. France*, 1937, **4**, 695.

calculated from weights of material taken. Good second-order rate-constants were calculated for the first 80% of chlorine displacement. These constants are in the left-hand part of Table 1.

TABLE 1. *Second-order titrimetric and spectroscopic rate-constants, and spectrophotometric product-compositions for the substitution of hydroxyl for chlorine by hydroxide-ion attack on the* trans-*chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *ion in aqueous methyl alcohol or in water.*

[" Titr." means by pH titration, and " Spec." means by spectrophotometry. In the rate measurements by spectrophotometry the optical density at 4900 Å was used, and the extinction coefficients, $\varepsilon_a = 40$ and $\varepsilon_\infty = 187$ in water, were taken as calibration points. The latter figure is calculated for aquo*iso*thiocyanato-products containing 76% of the *cis*-isomer. Rate-constants were calculated for the first 80% of reaction from the formula $k_2 = \{2{\cdot}303/t(b-a)\} \log_{10} \{a(b-x)/(b(a-x)\}$ sec.$^{-1}$ mole^{-1} l., or in case $b = a$, the formula $k_2 = x/ta(a-x)$ sec.$^{-1}$ mole^{-1} l., where a is the initial concentration of the complex cobalt ion, and b that of the hydroxide ion. The complex chloro-cation was supplied as bromide for the measurements in aqueous methyl alcohol, and as perchlorate for the measurements in water. Hydroxide ions were introduced as carbonate-free sodium hydroxide. The measurements of product-composition during the progress of the runs, as given in the last column of the Table, involved determinations of optical density at three wavelengths, 5800, 5300, and 4900 Å (cf. Sub-section 1.3).]

Run no.	MeOH (%) in solv.	*a* (mmole l.$^{-1}$)	*b* (mmole l.$^{-1}$)	k_2	Run no.	MeOH (%) in solv.	*a* (mmole l.$^{-1}$)	*b* (mmole l.$^{-1}$)	k_2	Products, *cis* (%)
Method, Titr. Temp., 0·00°.					*Method, Spec. Temp.,* 0·00°.					
10	87	3·02	5·85	0·098	37	0	2·08	2·08	0·357	79
11	86	2·77	6·57	0·104	38	,,	1·91	1·83	0·352	75
9	85	2·84	8·23	0·110	60	,,	1·76	2·69	0·371	75·5
7	83	3·07	6·12	0·113	59	,,	1·76	5·26	0·378	74
6	82	3·34	4·10	0·116	61	,,	1·77	10·90	0·311	75
					62	,,	1·76	21·72	0·348	76
17	0	3·15	5·93	0·347	63	,,	0·94	8·11	0·323	77
30	,,	2·46	3·48	0·350	64	,,	1·77	8·11	0·349	76
29	,,	2·35	6·69	0·368	65	,,	2·61	8·11	0·324	75·5
31	,,	2·49	7·92	0·374	66	,,	3·55	8·11	0·328	75
32	,,	2·45	9·60	0·365						
34	,,	2·45	11·11	0·349				Mean	0·339	75·8
			Mean	0·359	*Method, Spec. Temp.,* 10·05°.					
					68	0	2·29	6·05	1·41	74·5
					69	,,	4·02	6·05	1·28	75
					71	,,	6·06	6·05	1·49	73
					72	,,	1·86	3·86	1·54	72
					73	,,	1·97	1·96	1·53	75
					74	,,	1·95	8·74	1·55	76
								Mean	1·47	74·2
					Method, Spec. Temp., 20·00°.					
					81	0	3·92	3·92	6·11	73
					82	,,	3·24	3·24	6·65	72
								Mean	6·38	72·5

The spectrophotometric method depends on differences in the absorption spectra of the *trans*-chloro-cation, and of the *cis*- and *trans*-aquo-cations —aquo- and not hydroxy-cations, because reaction was followed by means of the spectra of acidified samples. These three spectra are among those shown in Fig. 1. Salts of the three cations, individually, and as binary pairs, were shown to obey the Beer–Lambert law at the relevant wave-lengths and concentrations.

The initial spectrum of the reaction is the spectrum of the *trans*-chloro-cation. It is not possible directly to observe a final spectrum corresponding to the completed displacement of chlorine, because of the commencement, at late times, of the second stage of hydroxylation. However, as the next Sub-section shows, we know the proportions in which the *cis*- and *trans*-aquo-cations are produced, and therefore can calculate, from the observed spectra of the separate cations, a spectrum corresponding to the completion of chlorine displacement. It is thus found that the greatest change in optical density between the *trans*-chloro-cation and the produced mixture of *cis*- and *trans*-aquo-cations occurs at

4900 Å, and therefore optical density at this wavelength was adopted as the indication of reaction progress.

As before, good second-order rate-constants were calculated for the first 80% of reaction. These constants are entered in Table 1. The spectrophotometric constants for 0° are slightly lower than the titrimetric constants for solvent water at that temperature, but, as mentioned above, we must expect the titrimetric method to give high values. The errors in the spectrophotometric method seem to be random. We must assume that they obscure the theoretically expected negative salt effect, which would, however, be small at the concentrations used. Nevertheless, the spectrophotometric constants have been determined over a range of reagent concentration great enough to leave no doubt that the alkaline hydrolysis is indeed a second-order reaction.

Most of the rates are not inconveniently high at 0°; but at 10° the general accuracy begins to be affected by errors of timing, and at 20° these are much the most serious errors. The Arrhenius equation which best fits the rate data for these three temperatures is $k_2 = B_2 e^{-E/RT}$ with $B_2 = 6{\cdot}6 \times 10^{13}$ sec.$^{-1}$ mole^{-1} l., and $E = 23{\cdot}2$ kcal./mole. But because

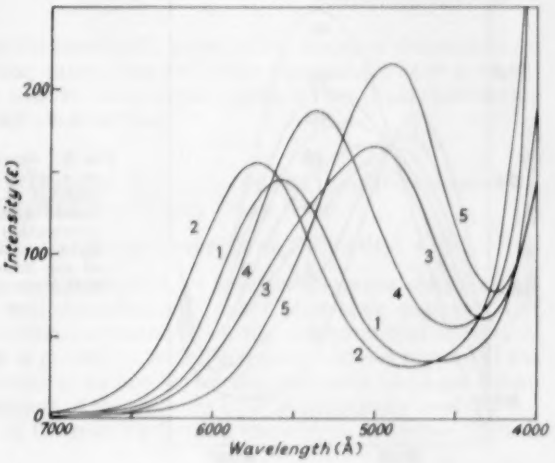


FIG. 1. *Spectrophotometric curves of extinction coefficients for halogeno- and aquo-isothiocyanatobis(ethylenediamine)cobalt*(III) *ions in water:*
(1) *trans*-[Co en$_2$(NCS)Cl]$^+$.
(2) *trans*-[Co en$_2$(NCS)Br]$^+$.
(3) *cis*-[Co en$_2$(NCS)Cl]$^+$.
(4) *trans*-[Co en$_2$(NCS)OH$_2$]$^{2+}$.
(5) *cis*-[Co en$_2$(NCS)OH$_2$]$^{2+}$

of the low accuracy of the measured rates at 20°, these parameters must be regarded as only roughly evaluated.

(1.3) *Steric Course.*—Werner preparatively converted the *trans*-chloro-cation, as thiocyanate, by means of concentrated potassium hydroxide, into the *trans*-hydroxy-cation, and, as dithionate, by means of concentrated aqueous ammonia, into the *cis*-hydroxy-cation,[2a] thereby making the stereochemistry of the formed hydroxy-cation apparently depend either on the anion of the complex cobalt salt or on the cation of the alkali. We therefore began our stereochemical investigation by allowing dilute solutions of the bromide, perchlorate, thiocyanate, and dithionate of the *trans*-chloro-cation to interact with dilute potassium and ammonium hydroxide. We found that, when the displacements of chlorine were substantially complete, the spectra of the solutions were practically identical. It has to be concluded that some condition is present in Werner's preparations which does not apply in our dilute solutions.*

When the absorption spectra of acidified reaction samples taken at different times are

* This is not simply that the thiocyanate of the *trans*-aquo-cation is the less soluble of the stereoisomeric thiocyanates, whilst the dithionate of the *cis*-aquo-cation is the less soluble of the isomeric dithionates, because a more than 50% yield is obtained in either type of preparation. It is possible that, in the concentrated alkali a bimolecular OH-exchange, with hydroxide ion as substituting agent, leads to reversible stereo-change between the hydroxy-cations, and a subsequent disturbance of the balance of the isomers by separation of one or the other, according to the available anion. We have left this matter undecided, but report the incidental observation that Werner's preparation of the *cis*-hydroxy-salt can be repeated with the modification of using lithium in place of ammonium hydroxide.

plotted together, all the curves go through a single point, as shown in Fig. 2, with the exception of the curve applying to " infinite time." This means that, except at late times, the one original coloured substance is being replaced, either by only one other, or by more than one under the condition that these are being formed in a strictly constant ratio. In other words, if both *cis*- and *trans*-hydroxy-products are being formed, then they are arising as primary products, and simultaneously, in reactions of identical kinetic order.

With our knowledge of the spectra of the separate substances involved, curves such as these can be analysed to give the ratio in which the reaction of the *trans*-chloro-cation is yielding the *cis*- and *trans*-hydroxy-cations. A particularly sensitive form of analysis, and one which we like to apply when the optical results are good enough, is to read, for each reaction sample, the optical density at three wavelengths, and then to solve the three simultaneous linear equations that should, by Beer's law, give these optical densities in terms of the unknown concentrations of the three coloured substances. The coefficients in the equations are obtained by measuring the extinction coefficients of the three pure

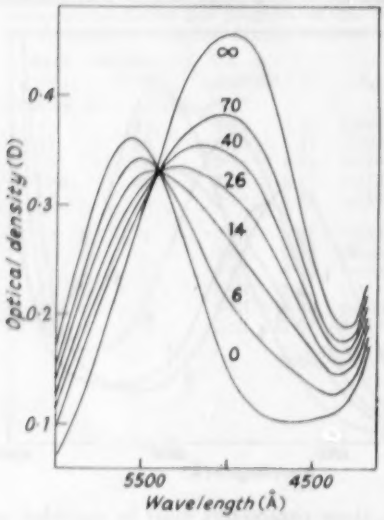


FIG. 2. *Spectrophotometric curves of optical density, in a cell of length 4 cm., of samples from Run 38, acidified at various times, given in minutes by the figures associated with the curves.* The common intersection shows that the products are being formed in constant proportions, and the deviation of the infinite-time curve that a subsequent reaction enters at late times.

substances at the same three wavelengths, the partial optical density due to any absorbing component being the product if its concentration, its extinction coefficient, and the path-length. The equations being solved for the concentrations, we have a check upon the method, inasmuch as the sum of the three concentrations should be the same for all reaction samples. The concentrations will give additionally the proportion of reaction which has occurred, and the ratio in which *cis*- and *trans*-hydroxy-products are present, in each of the samples taken. The extinction coefficients, which we have determined with pure salts and used in this way, are in Table 2; and, as an illustration of the method, its application to one run is set out in Table 3.

It was confirmed quite generally by this analysis that the *cis*- and *trans*-hydroxy-products are formed in constant ratio throughout reaction. The mean values thus obtained for the stereoisomeric compositions of the products of all the runs which were thus followed spectrophotometrically are collected in the last column of Table 1. The

TABLE 2. *Extinction coefficients* (ε *in cm.*$^{-1}$ *mole*$^{-1}$ *l.*) *as determined for pure salts in water at* 0°, *and used for the spectrophotometric measurement of composition.*

	λ (Å)	5800	5300	4900
10{	*trans*-$[Co\ en_2(NCS)Cl]^+$	122·6	110·3	40·0
	cis-$[Co\ en_2(NCS)OH_2]^{2+}$	37·7	145·3	216·2
	trans-$[Co\ en_2(NCS)OH_2]^{2+}$	100·3	185·1	99·6

TABLE 3. *Spectrophotometric analysis of run* 62.

{Solvent: water. Temp.: 0°. Initial concn. of *trans*-[Co en$_2$(NCS)Cl]$^+$ = 0·00176M, and of NaOH = 0·02172M. Samples were acidified, and made up to a 2-fold dilution with water, before measurement in a cell of length 4 cm. The observations are in the first four columns. In following columns, the calculated concentrations of *trans*-[Co en$_2$(NCS)Cl]$^+$, *cis*-[Co en$_2$(NCS)OH$_2$]$^{2+}$, and *trans*-[Co en$_2$(NCS)OH$_2$],$^{2+}$ called [A], [B], and [C], respectively, are in units 10^{-4} mole/l. The figures in the last two columns are 100([B] + [C])/([A] + [B] + [C]) and 100[B]/([B] + [C]), respectively.}

Time	Optical density			Calcd. concns.				Reactn.	*cis*
(sec.)	D_{5500}	D_{5300}	D_{4900}	[A]	[B]	[C]	Sum	(%)	(%)
77·2	0·320	0·450	0·353	4·78	2·68	1·12	8·58	44·3	71
94·2	0·311	0·461	0·390	4·53	3·21	1·01	8·75	48·2	76
112·2	0·299	0·468	0·412	4·07	4·37	1·17	8·70	53·2	75
131·0	0·289	0·470	0·429	3·79	3·72	1·16	8·67	56·3	76
153·2	0·270	0·480	0·462	3·08	4·12	1·40	8·60	64·2	75
174·2	0·259	0·491	0·498	2·73	4·62	1·37	8·72	68·7	77
209·4	0·240	0·502	0·533	2·02	5·05	1·61	8·68	76·9	76
249·0	0·232	0·520	0·573	1·63	5·54	1·69	8·86	81·6	77
319·2	0·216	0·521	0·602	1·28	6·01	1·55	8·84	85·5	79
								Mean *cis*-product:	76

essential result is that, in this definitely bimolecular substitution, the *trans*-chloro-cation is converted into 76% of the *cis*-hydroxy-cation, and 24% of its *trans*-isomer, at 0° in water. At higher temperatures the figures seem to move slightly towards each other, but further experiments on the temperature effect are desirable.

(2) *Kinetics and Products of the Reaction of Hydroxide Ion with* trans-*Bromoisothiocyanatobis(ethylenediamine)cobalt*(III) *Ion in Water:*

$$OH^- + \textit{trans}\text{-[Co en}_2\text{(NCS)Br]}^+ \longrightarrow \textit{cis}\text{- and } \textit{trans}\text{-[Co en}_2\text{(NCS)OH]}^+ + Br^-$$

(2.1) *Basic Chemistry.*—The *cis*- and *trans*-series of bromo*iso*thiocyanatobis(ethylenediamine)cobalt(III) salts are both well characterised. Apart from close analogies with corresponding salts of the two chloro*iso*thiocyanato-series, the configurational identity of the *trans*-bromo*iso*thiocyanato-salts is proved by their conversion, without rupture of the cobalt–nitrogen bond, into *trans*-bromoamminobis(ethylenediamine) salts, which are known as to configuration, because their isomers of the *cis*-series have been optically resolved.[2a]

The rest of the basic chemistry of the reaction forming the subject of Section (2) is as described in Sub-section (1.1).

(2.2) *Kinetics.*—This reaction of the *trans*-bromo-cation is faster than the corresponding reaction of the *trans*-chloro-cation. Consequently, we have not been able to use the titrimetric method for following the reaction of the bromo-compound, because of the increased error due to reaction in the course of titration. On the other hand, the spectrophotometric method, by reason of the increased spectral differences, is a little more accurate than before. The high rates of reaction of the bromo-cation precluded measurements at temperatures other than 0°.

The absorption curves on which the spectrophotometric method depends are in Fig. 1. The usual checks were made as to the applicability of Beer's law. For the determination of rate constants, we again used, as our index of the amount of reaction, the optical density at 4900 Å of acidified samples of the solution. The initial optical density was simply that due to the employed bromo-cation. Owing to the high rate of hydroxylation with bromine displacement, and the consequently reduced relative importance of the second stage of hydroxylation with displacement of the *iso*thiocyanato-group, a final optical density, to correspond to completion of displacement of the bromine, could be directly measured with fair accuracy; but we preferred to calculate it, from our knowledge of the spectra of the stereoisomeric aquo-cations, and of the proportions in which they are produced, as recorded in Sub-section (2.3).

Good second-order rate-constants, showing only a random scatter, presumably due to errors in timing the samples of these fast runs, could be calculated for the first 90% or so of

reaction. The constants for a number of runs are in Table 4. As they remain nearly the same over a 4-fold change in the initial concentration of each reactant, there can be no doubt that this hydroxyl substitution is a second-order process.

TABLE 4. *Second-order spectrophotometric rate-constants and product-compositions for the substitution of hydroxyl for bromine by hydroxide-ion attack on the* trans-*bromoisothiocyanatobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

[See explanation at the head of Table 1. The complex bromo-cation was supplied as perchlorate, and the hydroxide ion as sodium hydroxide. Rate measurements were based on the optical density at 4900 Å, with the calibrating extinction coefficients $\epsilon_0 = 32$ and $\epsilon_\infty = 194$, the latter figure being calculated for aquo*iso*thiocyanato-products containing 81% of the *cis*-isomer. The measurement of product-compositions during the progress of the runs was based on determinations of optical density at the wavelengths 5800, 5300, and 4600 Å.]

Run	a	b	k_2	Mean	Products (%)	
no.	(mmole/l.)		(sec.$^{-1}$ mole^{-1} l.)		*cis*	Mean
101	2·47	3·26	1·84		81	
102	1·43	1·62	1·76		83	
103	1·41	3·27	2·10	1·95	81	81·4
104	1·42	4·94	1·96		81	
105	1·42	6·27	2·17		81	
106	0·68	3·30	1·90		—	—

(2.3) *Steric Course.*—The absorption curves of acidified reaction samples all go through a common point. This shows that, if several coloured substances are being formed, then they are being produced in constant proportions. The analysis which gives the proportions in which the *cis*- and *trans*-hydroxy-products are formed, was made by reading the optical densities of the samples at three wavelengths, and then setting up simultaneous equations for them in terms of the unknown concentrations of the three coloured substances, the coefficients in the equations being given by the extinction coefficients, recorded in Table 5, which were measured in the pure substances at the same wavelengths. The general consistency of the method is better than in the previous application, as illustrated by the specimen analysis in Table 6.

TABLE 5. *Extinction coefficients* (ϵ *in cm.*$^{-1}$ *mole*$^{-1}$ *l.*) *as determined for pure salts in water at* 0°, *and used in the spectrophotometric measurement of composition.*

λ (Å)	5800	5300	4600
ϵ of *trans*-[Co en$_2$(NCS)Br]$^+$	154·6	84·4	36·3
ϵ of *cis*-[Co en$_2$(NCS)OH$_2$]$^{2+}$	37·7	145·3	151·5
ϵ of *trans*-[Co en$_2$(NCS)OH$_2$]$^{2+}$	100·3	185·3	57·7

TABLE 6. *Spectrophotometric analysis of run* 103.

{Solvent: water. Temp.: 0°. Initial concn. of *trans*-[Co en$_2$(NCS)Br]$^+$ = 0·00141M, and of NaOH = 0·00327M. Further explanation is at the head of Table 3, except that Br must be read for Cl.}

Time	Optical density			Calcd. concns.				Reactn.	*cis*
(sec.)	D_{5800}	D_{5300}	D_{4600}	[A]	[B]	[C]	Sum	(%)	(%)
57·8	0·340	0·292	0·187	4·76	1·79	0·33	6·88	30·8	85
85·4	0·311	0·314	0·214	4·02	2·34	0·53	6·88	41·6	81
115·6	0·288	0·333	0·239	3·43	2·84	0·66	6·93	50·5	81
157·6	0·259	0·352	0·266	2·73	3·40	0·78	6·91	60·5	81
211·0	0·235	0·374	0·294	2·10	3·96	0·92	6·98	69·9	81
268·6	0·210	0·380	0·305	1·55	4·23	1·04	6·82	77·3	80
361·6	0·190	0·393	0·321	1·05	4·56	1·19	6·80	84·6	79
511·0	0·173	0·411	0·345	0·06	5·03	1·26	6·89	91·3	80
" ∞ "	0·148	0·431	0·368	−0·06	5·49	1·46	6·89	100·9	79
								Mean *cis*-product:	81

The mean values of the stereoisomeric proportions of the products of the five runs thus examined are included in Table 4. The results show that in this certainly bimolecular displacement of halogen by hydroxide ion from the *trans*-bromo-cation in water at 0°, there are formed 81% of the *cis*-hydroxy-cation and 19% of its *trans*-isomer.

(3) *Kinetics and Products of the Reaction of the Hydroxide Ion with* cis-*Chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *Ion in Water :*

$$OH^- + cis\text{-}[Co\ en_2(NCS)Cl]^+ \longrightarrow cis\text{- and } trans\text{-}[Co\ en_2(NCS)OH]^+ + Cl^-$$

(3.1) *Basic Chemistry.*—This is as described in Sub-section (1.1).

(3.2) *Kinetics.*—This reaction is too rapid to be studied kinetically by the titrimetric method, and it is not an easy subject for the spectrophotometric method, because much of the absorption curve of the *cis*-chloro*iso*thiocyanato-cation lies about midway between the curves for the *cis*- and the *trans*-aquo*iso*thiocyanato-cations, with the result that the change of absorption during reaction is somewhat slight. However, the relevant absorption curves being as in Fig. 1, we have examined the kinetics of the reaction, using the optical density of acidified samples at 4700 Å as indicator of reaction progress. Owing to the large rate of chlorine displacement, the end of this process is not much overlapped by the beginning of thiocyanate liberation, and hence second-order rate-constants could be calculated over nearly the whole reaction. The mean rate-constants for several runs are in Table 7. Though they are not very precise, they apply to a sufficiently wide range of reactant concentrations to leave no doubt that a second-order reaction is under observation.

(3.3) *Steric Course.*—Owing to the smallness of the changes of absorption it was not possible in this case to carry out complete analyses during the course of reaction, based on the absorption at three wavelengths. The reaction was therefore run to completion at 0°, and the absorption was measured at a single wavelength, one favourable for distinguishing between the *cis*- and *trans*-aquo-isomers, *viz.*, 4900 Å. The extinction coefficient of the acidified reaction solution at this wavelength was 193·2, and from this and the extinction coefficients, given in Table 2, for the separate aquo-salts, it can be calculated that the

TABLE 7. *Second-order spectrometric rate constants for the substitution of hydroxyl for chlorine by hydroxide ion attack on* cis-*chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

[See explanation at the head of Table 1. The *cis*-chloro-cation was supplied as chloride, and the hydroxide ion as sodium hydroxide. For measurements of reaction progress based on optical densities at 4700 Å, the extinction coefficients $\varepsilon_0 = 125{\cdot}7$ and $\varepsilon_\infty = 159{\cdot}8$ were taken as providing end-values.]

Run no.	75	77	78	79	
a (mmole/l.)	2·25	2·24	3·12	4·54	
b (")	3·73	8·09	8·09	8·09	
k_2 (sec.$^{-1}$ mole^{-1} l.)	1·35	1·45	1·52	1·28	Mean : 1·40

mixture of isomers produced contained 80·3% of the *cis*-form. This figure is slightly low, because, in the completed run, owing to the overlapping of reaction stages, a small proportion of the aquo*iso*thiocyanato-cations will become replaced by the less absorbing diaquo-cations. By noting the approximate rate of this slow further change, it is possible to make a rough allowance for its effect on our result. By doing so, we obtain an adopted value of 82% for the proportion of *cis*-hydroxy-isomer formed in the first stage of bimolecular hydroxylation of the *cis*-chloro-cation by hydroxide ions in water at 0°.

(4) *Kinetics and Products of the Aquation of* trans-*Chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *Ion in Water :*

$$H_2O + trans\text{-}[Co\ en_2(NCS)Cl]^+ \longrightarrow \left\{ \begin{array}{c} cis\text{-}[Co\ en_2(NCS)OH_2]^{2+} \\ \rightleftarrows \\ trans\text{-}[Co\ en_2(NCS)OH_2]^{2+} \end{array} \right\} + Cl^-$$

As described in Sub-section (1.1), our examination of the stabilities of the complex salts, in the conditions concerned in the investigations on their alkaline hydroxylations, led us to study certain reactions which these salts undergo in water in the absence of alkali. These observations are described in Sections (4)—(6).

(4.1) *Kinetics.*—In water at raised temperatures the *trans*-chloro-cation undergoes

aquation in two steps: first the chlorine is replaced by a water molecule, and then the *iso*thiocyanato-group is similarly replaced. The first step is the faster, and its rate is independent of hydrogen ions at pH values of less than 5. The second step, however, is considerably retarded by hydrogen ions; and so, by working with acidities approaching that of pH 2, it becomes possible to ignore this step completely.

In these conditions the products of the aquation are simply the *cis*- and *trans*-aquo*iso*thiocyanato-salts. But these do not appear in the ratio in which they are formed, because they undergo reversible interconversion. This reaction is rapid, but not instantaneous; and therefore the aquo-isomers do not immediately appear in their equilibrium ratio, though at late times they attain these proportions. In fact, they do not appear in any constant ratio during the progress of reaction, and we are consequently precluded from measuring reaction progress by the change of optical density at a fixed wavelength. What we have done, therefore, is, first, to follow the changes of optical density at the three wavelengths, 5800, 5300, and 4900 Å, then, with the aid of the constants in Table 2, to set up simultaneous equations for these optical densities in terms of the unknown concentrations of the three coloured substances, and, finally, to extract from these equations the one root of importance for the kinetics of the aquation, *viz.*, that representing the concentration of surviving chloro-cation.

The disappearance of the chloro-cation follows the first-order rate-law. Our rate-constants for this reaction are in Table 8. They fit the Arrhenius equation $k_1 = B_1 e^{-E/RT}$, with $B_1 = 8{\cdot}5 \times 10^{14}$ sec.$^{-1}$, and $E = 30{\cdot}4$ kcal./mole.

(4.2) *Steric Course.*—We failed to determine this for the reason that the specific rate of interconversion of the aquo-products (Section 6) is about 10—15 times greater than that of their collective formation. This means that only a somewhat small fraction of the material in any sample is causing a departure of the composition from the equilibrium composition. Thus the observed departures were too small, in relation to the errors of

TABLE 8. *First-order spectrophotometric rate constants* (k_1 *in* sec.$^{-1}$) *for the aquation of the* trans-*chloroisothiocyanatobis(ethylenediamine)cobalt*(III) *ion in* 0·0070N-*aqueous perchloric acid* (pH 2·16).

[The complex cation was supplied as perchlorate. Optical densities at 5800, 5300, and 4900 Å were measured, and concentrations were then calculated with the aid of the extinction coefficients of Table 2.]

Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1	Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1	Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1
At 45·0°				At 70·6°				At 89·9°			
53	1·97	0·106	0·113	45	2·27	3·93	4·04	51	2·00	40·3	42·8
54	2·82	0·114		48	3·06	4·00		52	2·97	43·4	
55	3·90	0·114		49	4·06	3·97		47	4·16	43·5	
56	4·96	0·118		46	4·98	4·28		50	5·09	43·7	

measurement, to justify the long extrapolation which would be required in order to give the composition of freshly formed aquation products.

(5) *Kinetics and Products of the Aquation of* trans-*Bromoisothiocyanatobis(ethylenediamine)cobalt*(III) *Ion in Water:*

$$H_2O + \textit{trans}\text{-}[Co\ en_2(NCS)Br]^+ \longrightarrow \left\{ \begin{array}{c} \textit{cis}\text{-}[Co\ en_2(NCS)OH_2]^{2+} \\ \rightleftarrows \\ \textit{trans}\text{-}[Co\ en_2(NCS)OH_2]^{2+} \end{array} \right\} + Br^-$$

(5.1) *Kinetics.*—The general conditions applying to this aquation are as described above for the chloro-cation, except that the aquation of the bromo-cation goes about 4 times faster. Thus its rate, and that of the following isomerisation, are more nearly comparable; and therefore the proportions in which the aquo-products appear drift much more in the course of reaction. It is thus all the more necessary to use three wavelengths, rather than one, for following the disappearance of the bromo-cation.

From observed optical densities at 5800, 5300, and 4600 Å, good first-order rate

constants for the aquation were obtained. These are given in Table 9. They agree with the formula $k_1 = B_1 e^{-E/RT}$ in which $B_1 = 2{\cdot}1 \times 10^{15}$ sec.$^{-1}$ and $E = 30{\cdot}1$ kcal./mole.

TABLE 9. *First-order spectrometric rate constants* (k_1 *in sec.*$^{-1}$) *for the aquation of the* trans-*bromoisothiocyanatobis(ethylenediamine)cobalt*(III) *ion in* 0·0070N-*aqueous perchloric acid* (pH 2·16).

[The complex cation was supplied as perchlorate. Optical densities at 5800, 5300, and 4600 Å were measured, and concentrations were then calculated with the aid of the extinction coefficients of Table 5.]

Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1	Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1	Run no.	Initial Co salt (mmole/l.)	10^5k_1	Mean 10^5k_1
	At 62·6°				At 70·6°				At 89·9°		
113	2·23	5·81	5·78	110	2·18	16·5	16·5	117	2·99	158	161
112	2·94	5·63		108	3·02	16·2		111	4·09	162	
114	4·29	5·74		109	4·28	16·7		116	4·80	164	
115	5·23	5·92									

(5.2) *Steric Course.*—The specific rate of aquation of the *trans*-bromo-cation, and the specific rate of approach to equilibrium of the formed aquo-isomers, are alike to within a factor of 3. It follows that, if the *cis*- and *trans*-aquo-cations are formed in one ratio, but finally come into equilibrium at a different one, we should be able to observe a substantial part of this drift from the one isomer ratio to the other, in the course of the aquation process.

This ratio does indeed drift. The spectrophotometric method of analysis, with which we follow the kinetics of aquation, has, because of the drift, to be so elaborated that it gives not only the concentrations of the surviving bromo-cation, but also those of the separate *cis*- and *trans*-aquo-cations; and thus the analysis shows the drift, as illustrated in Table 10.

The simplest way to use these drifts in the measured ratio of isomers present in order to deduce the ratio in which the *cis*- and *trans*-aquo-cations are initially *formed*, would be to extrapolate the measured ratios back to zero time. However, an extrapolation of the length involved, if made empirically, would be somewhat hazardous; and it is safer to "guide" it theoretically by fitting a curve of the right functional form to the data. This we can do with the aid of rate-constants given in Sections (5.1) and (6).

TABLE 10. *Spectrophotometric analysis of run* 116.

[Solvent: 0·0070N-aqueous perchloric acid (pH 2·16). Temp.: 89·9°. Initial concn. of *trans*-$[Co\,en_2(NCS)Br]^+[ClO_4]^-$ = 0·00480M. Undiluted samples examined in cell of length 1 cm. See also explanation at head of Tables 3 and 6.]

Time (sec.)	Optical density			Calc. concns.				Reactn. (%)	*cis* (%)
	D_{5800}	D_{5300}	D_{4600}	[A]	[B]	[C]	Sum		
112	0·658	0·459	0·228	38·8	4·2	3·6	46·6	16·8	54
195	0·620	0·488	0·261	34·8	6·8	4·9	46·5	25·3	58
281	0·559	0·515	0·305	29·2	10·7	5·8	45·8	36·2	65
378	0·520	0·545	0·343	25·2	13·8	6·8	45·8	45·0	67
481	0·470	0·568	0·381	20·7	17·1	7·5	45·3	54·4	70
589	0·432	0·599	0·423	16·8	20·5	8·3	45·6	63·1	72
705	0·396	0·607	0·448	14·0	22·9	8·0	45·0	68·9	74
860	0·359	0·624	0·484	10·9	26·1	7·8	44·9	75·7	77
1009	0·325	0·641	0·503	7·5	27·7	9·0	44·3	83·1	75
1199	0·306	0·659	0·540	5·9	30·8	8·4	45·0	86·8	79

Let f be the fraction of *cis*-aquo-isomer in the total aquo-isomers *present* at any time t. Then the precise way in which f will vary with time between its limits, f_0 at $t = 0$, and f_∞ at $t = \infty$, will depend on the rates of aquation and isomerisation, in particular on the specific rate k_a of total aquation of the bromo-cation and the total specific rate $k_1 + k_{-1}$ of the approach, by reversible interconversion of the aquo-isomers, to their equilibrium. The functional form of the variation with time of the isomer ratio present, as measured by f, is expressed in the following equation:

$$\frac{f - f_\infty}{f_0 - f_\infty} = \frac{k_a}{(k_1 + k_{-1}) - k_a} \cdot \frac{\exp(-k_a t) - \exp[-t(k_1 + k_{-1})]}{1 - \exp(-k_a t)}$$

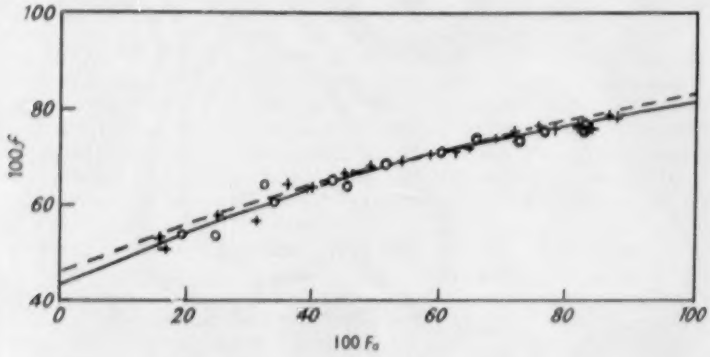
The derivation of this formula is outlined below. While the composition of the isomers present, as measured by f, is changing thus, the fraction F_a, measuring the total progress of aquation, is increasing with time according to the formula

$$F_a = 1 - \exp(-k_a t)$$

By eliminating t between these equations we can treat f as a function of F_a, as is done in Fig. 3. The equation connecting f with F_a contains only rate constants, which we have measured, f_∞, which we can measure, and one adjustable parameter f_0. This f_0 measures the ratio of isomers initially *formed*, and is our real unknown: we choose it so as to make the theoretical curve for f fit the data as well as may be.

Experimental values of f are plotted against F_a for a number of runs in Fig. 3. Two temperatures are involved, but the scatter of points on account of analytical error is greater than the temperature effect. Theoretical curves are plotted, according to the

FIG. 3. *Theoretical curves,* (——) *for* 62·6° *and* (– – –) *for* 89·9°, *and experimental values,* ○ *for* 62·6° *and* + *for* 89·9°, *for the percentage* $100f$ *of* cis-*aquo-isomer contained in the total aquo-isomers present at various percentage degrees of progress* $100F_a$ *of aquation of* trans-$[Co\ en_2(NCS)Br]^+$ *in dilute aqueous perchloric acid.* The intercepts on the f axis give the proportions in which the aquo-isomers are formed by aquation.



above equations, for the two temperatures. (The flatter curve applies to the higher temperature, for which the isomerisation is less fast relatively to the aquation.) The experimental parameters used in the equations in order to construct these curves are derived from Sections (5.1) and (6), and are in the middle three columns of Table 11. The last column of this Table gives the results of these "guided extrapolations," *viz.*, the

TABLE 11. *Rate data used to calculate the steric course of aquation of the* trans-*bromoisothiocyanatobis(ethylenediamine)cobalt*(III) *ion from analytical observations on aquation products undergoing isomerisation concurrently with production. Calculated steric course of the aquation.*

	Experimental			Calcd.
Temp.	k_a (sec.$^{-1}$)	$k_1 + k_{-1}$ (sec.$^{-1}$)	f_∞	f_0
62·6°	$5{\cdot}78 \times 10^{-6}$	$16{\cdot}4 \times 10^{-6}$	0·81	0·43
89·5	—	340×10^{-6}	0·84	—
89·9	161×10^{-6}	(356×10^{-6}) *	(0·84) *	0·46

* Extrapolated for temperature.

values of f_0 required to give the fit shown in Fig. 3. It would appear that there is considerable stereo-change in this aquation: at 63°, the *trans*-bromo*iso*thiocyanato-cation produces 43% of the *cis*-aquo*iso*thiocyanato-cation, and 57% of its *trans*-isomer.

In order to derive the above equation for f, we first set down the concentration dx_1 of total aquo-products *formed* during an element of time dt_1 at t_1 :

$$dx_1 = k_a [\exp(-k_a t_1)]dt_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The concentration of *cis*-isomer contained in this element of aquo-products, when freshly formed, will be $f_0 dx_1$. But, on account of the reversible isomerisation, at a later time t, the concentration of *cis*-isomer in this element of formed material dx_1 will have changed to $f dx_1$, where

$$(f - f_\infty)/(f_0 - f_\infty) = \exp[-(k_1 + k_{-1})(t - t_1)] \quad . \quad . \quad . \quad . \quad (2)$$

This concentration $f dx_1$ must be expressed in terms of the differential dt_1 rather than of dx_1, by means of (1) and (2), and it must then be integrated from $t_1 = 0$ to $t_1 = t$, in order to obtain the total concentration of *cis*-isomer *present* at time t. We do not set down these steps as they are purely mechanical. The total concentration of aquo-isomers present at time t is given by (3) :

$$aF_a = a[1 - \exp(-k_a t)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The ratio of these concentrations is f, the equation for which, given on p. 1701, contains f_0, because of the use of equation (2). In the application of this equation, f is treated as known, and f_0 as the unknown.

(6) *Rate and Equilibrium in the Reversible Isomerisation of the* cis- *and* trans-*Aquoisothiocyanatobis(ethylenediamine)cobalt*(III) *Ions in Water :*

$$cis\text{-} \rightleftharpoons trans\text{-}[Co\ en_2(NCS)OH_2]^{2+}$$

In warm aqueous solutions acidified with perchloric acid, each of the aquo*iso*thiocyanato-isomers undergoes conversion into the other. The composition thus tends to an equilibrium; but at late times this situation may be disturbed by a slow incursion of an aquation process in which a second water molecule enters the complex, with ejection of the *iso*thiocyanato-group. However, this aquation is retarded by hydrogen ions; and so, by working at acidities near 0·01N or higher, it can be made unimportant.

Using the pure salts *cis*-$[Co\ en_2(NCS)OH_2]^{2+}S_2O_6^{2-},3H_2O$ and *trans*-$[Co\ en_2(NCS)OH_2]^{2+}(Br^-)_2,2H_2O$, we have measured spectrophotometrically the rate of isomerisation of either isomeric cation, and the ratio of their concentrations at equilibrium. The index of reaction progress was the optical density at 4800 Å. The incursion of a small amount of aquation at late times probably had no effect on the rate measurements. However, in the long-period runs, which were made in order to determine equilibrium composition, it may have led to low estimates of the proportion of the more absorbing *cis*-isomer, since the diaquo-cation is a relatively weak absorber at the wavelength used. Of these long-period experiments, those which started with the *trans*-isomer are expected to have produced the more accurate results.

The kinetics were those of a balanced reaction of first order in both directions. The sum $k_1 + k_{-1}$ of the rate constants of the opposing reactions, *i.e.*, the specific rate of approach to equilibrium, could be calculated directly from the optical densities, by means of the following equation :

$$k_1 + k_{-1} = (2{\cdot}303/t) \log_{10} (D_0 - D_\infty)/(D_t - D_\infty)$$

The measured specific rate-sums $k_1 + k_{-1}$ are in Table 12. They show that the rate of isomerisation is independent of the concentration of hydrogen ions within the range of our measurements. The measured equilibrium compositions are also in Table 12. They show that the rate-ratio k_{-1}/k_1 is approximately 5.

This isomeric change may be intramolecular, or it may be a substitution with stereochange; but we cannot know which it is, nor, if the latter alternative is correct, how much substitution simultaneously occurs without stereo-change, in the absence of measurements,

which have not yet been made but are being undertaken, of the rate of water-exchange with isotopically labelled solvent water.

TABLE 12. *First-order rate-constants* ($k_1 + k_{-1}$ *in sec.*$^{-1}$) *of approach to equilibrium, and stereoisomeric composition at equilibrium, in the reversible interconversion of* cis- *and* trans-*aquoisothiocyanatobis(ethylenediamine)cobalt*(III) *ions in dilute aqueous perchloric acid.*

Run no.	Temp.	pH	Initial confign.	Initial [Co salt] (mmole/l.)	Rate: 10^5 ($k_1 + k_{-1}$)		Equilm.: *cis* (%)	
58	62·6°	2·16	*trans*	3·63	16·1	16·4	83	82
67	,,	0·28	,,	3·62	16·7		83	
83	,,	1·70	*cis*	4·48	13·9		79	
84	,,	0·33	,,	4·68	16·4		79	
57	89·5	2·16	*trans*	3·66	340		84	

(7) *Summary and Discussion.*

The main results recorded in the foregoing are collected in Table 13.

As noted in Part I, it is a pecularity of the octahedral geometry of the complexes under discussion, that complete correlation does not exist between microchemical stereo-change associated with individual molecular acts of substitution, a form of stereo-change that can be reduced to the concept of "edge-displacement," and observable changes of stereochemical classification in actual experiments on substitution. If the compound substituted is a *trans*-isomer, then, and then only, the correlation is complete: all molecular acts of substitution that proceed without stereo-change then give a *trans*-product, and all those that involve stereo-change yield a *cis*-product. But if the compound substituted is the *cis*-isomer, then, although all molecular acts of substitution that proceed without stereo-change give the *cis*-product, those that involve stereo-change may give either *cis*- or *trans*-products; and thus the proportion of *cis*-product found macrochemically is only an

TABLE 13. *Rate and steric course of reactions in water of bis(ethylenediamine)cobalt*(III) *ions containing the* isothiocyanato-*ligand.*

Reaction type	Kinetic order	Displaced group (X)	Temp.	Rate-constant	Product ratios (%) *cis*	*trans*
(*A*) *cis*- or *trans*-[Co en$_2$(NCS)X]$^+$ + OH$^-$ ⟶ *cis*- and *trans*-[Co en$_2$(NCS)OH]$^+$ + X$^-$				k_2 (sec.$^{-1}$ mole^{-1}/l.)		
S_N2	2	*trans*-Cl	0·0°	0·34	76	24
	,,	,,	10·0	1·47	74	26
	,,	,,	20·0	6·38	72·5	27·5
	,,	*trans*-Br	0·0	1·95	81	19
	,,	*cis*-Cl	0·0	1·40	82	18
(*B*) *trans*-[Co en$_2$(NCS)X]$^+$ + OH$_2$ ⟶ *cis*- and *trans*- [Co en$_2$(NCS)OH$_2$]$^{2+}$ + X$^-$				k_1 (sec.$^{-1}$)		
Aquation	1	*trans*-Cl	45·0	0·113 × 10^{-5}	—	—
	,,	,,	70·6	4·04 ,,	—	—
	,,	,,	89·9	42·8 ,,	—	—
	,,	*trans*-Br	62·6	5·78 ,,	43	57
	,,	,,	70·6	16·5 ,,	—	—
	,,	,,	89·9	161 ,,	46	54
(*C*) *cis*- or *trans*-[Co en$_2$(NCS)X]$^{2+}$ ⟶ *cis*- and *trans*-[Co en$_2$(NCS)X]$^{2+}$				($k_1 + k_{-1}$)(sec.$^{-1}$)		
Isomerisation	1	*cis*- or *trans*-OH$_2$	62·6	16·4 × 10^{-5}	81	19
	,,	*trans*-OH$_2$	89·5	340 ,,	84	16

upper limit to the proportion in which configuration is retained in the molecular transactions, whilst the proportion of *trans*-product found is a lower limit to the proportion in which stereo-change accompanies the molecular processes.

Of the three types of reaction for which stereochemical results in kinetically definite conditions are here reported, the only one of which the mechanism is well established is the

alkaline hydrolysis (*A*), which is certainly a bimolecular nucleophilic substitution S_N2.* Discussion in the remainder of this Section will be confined to reactions of this type. The aquation process (*B*) will be discussed in Part VI.

In carbon chemistry, S_N2 substitutions produce quantitative inversion of configuration, independently of the constitutional details of the system. If an analogous rigid rule held for cobalt substitutions, then, with all allowances made for the latitude with which, as recalled above, we must translate macroscopic stereochemical findings into molecular terms, it would still be true that a *trans*-halogeno-factor would give 100% of the *cis*-hydroxy-product in an S_N2 substitution. As Table 13 shows in two examples, this is not true. And the molecular interpretation of the actual results obtained in these examples is that, whilst most of the individual molecular encounters resulting in substitution do produce a stereo-change, a significant fraction of them effect substitution with retention of configuration.

It thus appears that in bimolecular octahedral substitutions no such sharp rule governs steric direction, as applies in the field of tetrahedral substitutions. Whether some less extreme form of the same rule applies, or, if not, what constitutional factors control the course of reaction, must be left for further experiment to determine.

(8) *Preparations.*

trans-Dichlorobis(ethylenediamine)cobalt(III) chloride, the starting material for many of the following preparations, was obtained as described by Bailar,[5] and crystallised twice from aqueous hydrochloric acid. For some experiments it was further purified by extraction with, and crystallisation from, well-dried methyl alcohol in which the tris(ethylenediamine) salt, present as an impurity, is insoluble (Found : C, 16·7, 17·0, 17·1; H, 5·5, 5·5, 5·6; Cl, 37·7, 37·2. Calc. for $C_4H_{16}N_4Cl_2Co$: C, 16·8; H, 5·6; Cl, 37·3%).

Salts of *cis*- and *trans*-chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) were prepared as Werner describes.[5a] The bromide of the *trans*-series was crystallised from water when required only as starting point for further preparations, but was recrystallised from dry methyl alcohol when required for measurements (Found : C, 17·1, 17·1; H, 4·7, 4·9. Calc. for $C_5H_{16}N_5SClBrCo$: C, 17·0; H, 4·6%). On treatment of a saturated solution of the bromide in water with a small excess of 72% perchloric acid, the *trans*-perchlorate separated, which was recrystallised from aqueous ethyl alcohol, but could not be analysed by combustion, because of the violence of its pyrolysis. By mixing a saturated aqueous solution of the bromide with one of potassium thiocyanate, the thiocyanate of the *trans*-series was obtained; it was recrystallised from water. The crude chloride of the *cis*-series was converted into the *cis*-perchlorate by grinding it with 72% perchloric acid, and then triturating the salt which separated again with perchloric acid. This salt was reconverted into the *cis*-chloride by adding concentrated hydrochloric acid to its concentrated solution in warm water; the salt formed was crystallised from aqueous ethyl alcohol.

trans-Dibromobis(ethylenediamine)cobalt(III) bromide was prepared by Werner's method,[5a] and after trituration with concentrated hydrobromic acid was obtained as its hydrogen bromide adduct, from which the loosely bound hydrogen bromide was removed by washing the crystals

* Interpretation of the second-order kinetics by an assumed extraction by the basic reagent of a nitrogen-bound proton of an ethylenediamine group, to give a more easily aquated complex ion, is considered to be excluded by the absence of a relation between bimolecular rate and base-strength (cf. Part II).

Our view that the second-order alkaline reaction is a bimolecular substitution S_N2, not dependent on preliminary conjugate-base formation, has very recently been contested by Pearson, Mecker, and Basolo,[4] on the ground that replacement, in cations such as *trans*-dichlorobis(ethylenediamine)cobalt(III), of the bis(ethylenediamine) by tetrapyridyl or bis-2 : 2′-dipyridyl ligands, which have no nitrogen-bound hydrogen, leads to a ready aquation which is unaccelerated by alkali up to pH 9·2. We think that a greatly increased prominence of unimolecular hydrolysis in the presence of the aromatic ligands is to be expected for the known reason for which one finds it on passing from a *n*-alkyl to a benzyl halide, *viz.*, participation of aromatic π-electrons. The high rates observed, especially with the dipyridyl complexes, strongly suggest that the above-named authors got their results by promoting a mechanism, rather than by suppressing one. Moreover, as will be shown in Part VI, they could have obtained at least as great a degree of alkali-independence by retaining the ethylenediamine residues and simply changing the *trans*-group (to a nitro-group moreover, which, by their mechanism, should favour alkali-sensitivity).

[4] Pearson, Mecker, and Basolo, *J. Inorg. Nuclear Chem.*, 1955, **1**, 341.
[5] See Fernelius, *Inorg. Synth.*, 1946, **2**, 233.

successively with water (a small amount), ethyl alcohol, and ethyl ether, and then heating at 110°. For some experiments, this salt was freed from its main impurity, the tris(ethylenediamine) salt, by extraction with, and crystallisation from, well-dried methyl alcohol.

Salts of the *trans*-bromo*iso*thiocyanatobis(ethylenediamine)cobalt(III) series were prepared by Werner's method [2a] from the above dibromo-bromide. The thiocyanate and the bromide were crystallised from water. The perchlorate was prepared from the thiocyanate by grinding the latter with concentrated perchloric acid. It was also prepared by treating a concentrated aqueous solution of the bromide with 72% perchloric acid, and crystallising from water the salt which separated (Found: C, 14·4; H, 4·0. Calc. for $C_5H_{16}O_4N_5SClBrCo$: C, 14·4; H, 3·9%).

Salts of the *trans*-hydroxy- and *trans*-aquo-series were also prepared by Werner's methods.[2a] *trans*-Chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) thiocyanate was dissolved in warm 25% aqueous potassium hydroxide, and the *trans*-hydroxy*iso*thiocyanatobis(ethylenediamine)-cobalt(III) thiocyanate, which separated slowly from the cooled solution, was washed with ethyl alcohol and ethyl ether, and recrystallised from a small amount of dilute aqueous potassium hydroxide (Found: C, 21·6, 21·6; H, 5·9, 5·6; H_2O, 6·6. Calc. for $C_6H_{17}ON_6S_2Co,H_2O$: C, 21·6; H, 5·8; H_2O, 5·5%). The absorption spectrum from 7000 to 3850 Å of an acidified aqueous solution of this salt was identical with that of a solution prepared in equivalent concentration from the aquo-salt next to be mentioned. A concentrated aqueous solution of the hydroxy-salt was mixed with one of bromine-free hydrogen bromide in very slight excess. On evaporation at low pressure over sulphuric acid, *trans*-aquo*iso*thiocyanatobis(ethylenediamine)cobalt(III) bromide separated as its dihydrate (Found: C, 13·0; H, 5·0; H_2O, 11·9. Calc. for $C_5H_{18}ON_5SBrCo,2H_2O$: C, 13·3; H, 4·9; H_2O, 12·0%).

Werner's method [2a] of preparing salts of the *cis*-hydroxy- and *cis*-aquo-series gave low and variable yields in our hands. He made the dithionate of the hydroxy-series by treating *trans*-chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) dithionate with concentrated aqueous ammonia; and from the hydroxy-salt he generated the dithionate of the aquo-series by addition of acetic acid. He mentions that, unless the original chloro-salt is very pure, the reaction takes an unwanted direction. Though we are not convinced that its formation has much to do with the final stages of purification of the chloro-salt, we confirm that a by-product is formed, often in large amount; and we have identified it, by analysis, and by its absorption spectrum, as *cis*-chloroamminobis(ethylenediamine)cobalt(III) dithionate. Because of the difficulties of this method, we have prepared *cis*-hydroxy- and *cis*-aquo-salts with the aid of an ion-exchange column [6] from *cis*-chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) chloride. A solution of this (5·5 g.) in water (115 ml.) was passed through a column, 60 cm. × 2 cm., of Amberlite IRA-400 in hydroxide form at a rate of 5 ml./min. The elutriant was acidified to pH 4 by addition of aqueous dithionic acid, freshly prepared from barium dithionate and sulphuric acid, and was evaporated under reduced pressure to 15—20 ml., and then set to crystallise after being warmed to 40° and having some ethyl alcohol added. The orange salt which separated was the nearly pure dithionate trihydrate of the *cis*-aquo-series, and by addition of more ethyl alcohol a further quantity of the same salt in a less pure form could be obtained from the purple solution, which contained the *trans*-isomeride. The first crop of the *cis*-salt was further purified by two more crystallisations from aqueous ethyl alcohol, the last of which produced no further change in the absorption spectrum (yield 2 g.; a further 1·8 g. were obtained by working up residues). The *salt* was dried in a vacuum over sulphuric acid, and then left in air to regenerate the trihydrate {Found: Co, 12·5, 12·4, 12·6, 12·6; S, 20·4; H_2O, 15·2. $[Co\,en_2(NCS)OH_2]S_2O_6,3H_2O$ requires Co, 12·9; S, 20·5; H_2O, 15·3%}. This salt on gentle dehydration loses only its $3H_2O$ of crystallisation, which it can recover by exposure to the air; but on stronger dehydration (as in the above analysis) it loses also its H_2O of constitution, and becomes converted into the dinuclear salt, *diisothiocyanatotetrakis(ethylenediamine)dicobalt*(III) *dithionate*, which on exposure to air takes up half the total amount of water lost, to form its tetrahydrate {Found: Co, 13·5; H_2O, 8·6. $[Co_2\,en_4(NCS)_2](S_2O_6)_2,4H_2O$ requires Co, 13·6; H_2O, 8·3%}. The absorption spectrum of this salt is naturally quite different from that of the mononuclear parent. The latter was converted into the thiocyanate of the *cis*-aquo-series, which is an anhydrous salt, by treatment of a concentrated aqueous solution of the dithionate with ammonium thiocyanate, and crystallisation of the resulting thiocyanate from water.

(9) *Methods of Measurement.*

For the alkaline hydrolytic runs, the weighed complex salt, dissolved in the solvent, aqueous methyl alcohol, or boiled-out distilled water, and also carbonate-free standard aqueous sodium

[6] Basolo and Steringer, *J. Amer. Chem. Soc.*, 1950, **72**, 5748.

hydroxide, and the water needed to adjust the volume of the reaction mixture, were separately brought to thermostat temperature, and then the reaction solution was made up. Timed samples, withdrawn by an appropriately jacketed, fast-running, 5 ml. pipette, were delivered into excess of aqueous perchloric acid.

In titrimetric analysis, this was a measured amount of standard acid, and the resulting solution was titrated with sodium hydroxide by using a glass electrode and calomel half-cell. In spectrophotometric analysis, the reaction samples were delivered into acid contained in 10 ml. standard flasks and, after making up to the marked volume, the absorption of light was measured, at one or more wavelengths, by means of a Unicam Quartz spectrophotometer SP 500.

For the aquation runs the sealed-tube method was used. The reaction solution was made up, from the weighed salt, water, and aqueous perchloric acid, at room temperature, and the set of tubes was then charged and simultaneously put into the thermostat. As soon as thermal equilibrium had been reached, one tube, and after timed intervals other tubes, were withdrawn, and cooled in solid carbon dioxide and alcohol in order quickly to stop the reaction. Their contents were then brought up to room temperature and analysed spectrophotometrically.

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336. *Mechanism, Kinetics, and Stereochemistry of Octahedral Substitutions. Part V.* Bimolecular Basic Hydrolysis and Aquation of Some Halogeno- and Nitrato-amminobis(ethylenediamine)cobalt*(III) *Ions.*

By R. S. NYHOLM and M. L. TOBE.

This paper continues the report on the steric course, in kinetically controlled conditions, of bimolecular nucleophilic substitution at octahedral cobalt. The present examples relate to the displacement by attacking hydroxide ions in solvent water of halogeno- or nitrato-ligands from halogeno- or nitrato-amminobis(ethylenediamine)cobalt(III) ions. The reactions are bimolecular, totally and with respect to each of the partial reactions leading to the stereoisomeric products, which underwent neither isomeric change nor further substitution under the conditions of their formation. At 0° the *trans*-chloro-cation gave 76%, the *cis*-chloro-cation 84%, the *cis*-bromo-cation 85%, and the *cis*-nitrato-cation 86% of *cis*-isomer, in the mixture of *cis*- and *trans*-hydroxy-isomers formed. When the *d-cis*-chloro-cation was employed the hydroxy-product contained 60% of the *d-cis*-isomer of like configuration, and 24% of its optical enantiomer, besides 16% of the *trans*-isomer. With the *d-cis*-bromo-cation the proportions of the same three products were 58%, 26%, and 15%, respectively. With the *l-cis*-bromo-cation the proportions were 27%, 58%, and 15%, respectively; and it is now the second of the three isomers which has a configuration resembling that of the initial halogen compound. Apart from the additional particulars furnished by the use of optically active compounds in the present series, these stereochemical findings, applying to reactions of a number of cations characterised by the presence of the ammonia ligand, closely resemble those reported in the preceding paper for reactions of a series of cations characterised by the presence of the *iso*thiocyanato-ligand. The directing effects of these two ligands on the substitutions are, therefore, either negligible or equal; and so the question of the degree of importance attaching to orienting effects, by ligands present already, on bimolecular octahedral substitutions is brought into the foreground.

The rates of the aquations which the above halogeno- and nitrato-cations undergo in aqueous acidic solutions have been measured, though these reactions are detectably reversible in the conditions used.

THIS paper describes an investigation of the kinetics and stereochemistry of some further bimolecular substitutions, in which an attacking hydroxide ion replaces a ligand in various

* Part IV, preceding paper.

bis(ethylenediamine)cobalt(III) cations, containing a characteristic unreplaced group. The latter group is the ammonia ligand in the present examples. The displaced groups are the chloro-, bromo-, and nitrato-ligands. The complex cations were examined in *trans*-, *DL-cis*, or *D*- or *L-cis*-forms.

(I) *Kinetics and Products of the Reaction of Hydroxide Ion with the* trans-*Chloroamminobis(ethylenediamine)cobalt*(III) *Ion in Water:*

$$OH^- + \textit{trans}\text{-}[Co\ en_2NH_3Cl]^{2+} \longrightarrow \textit{cis}\text{- and } \textit{trans}\text{-}[Co\ en_2NH_3(OH)]^{2+} + Cl^-$$

(1.1) *Basic Chemistry.*—The *cis*- and the *trans*-series of salts of chloroamminobis(ethylenediamine)cobalt(III) are well characterised, and their configurations are made certain by the optical resolution of the *cis*-salts.[1]

There are a number of chemical differences of analytical importance between the ammino-cations and the *iso*thiocyanato-cations discussed in the preceding paper. The ammino-ligand does not interact with silver ions. This makes available the method of following halogen displacement by silver titration of the produced halide ion, in acidified samples of the reaction solution. Actually, this method is not convenient for following the alkaline hydrolysis of the *trans*-chloroammino-cation, because of the high reaction rate; but it was used in the study of the more slowly reacting *cis*-chloroammino-cation.

The ammino-ligand is not displaced at all in dilute aqueous alkali at 0°, the conditions in which we have investigated the kinetics of displacement of the halogen; *i.e.*, there is no detectable second step of hydroxylation in these conditions. This meant that, in following the kinetics of the chlorine displacement by the spectrophotometric method, we were able to use the " infinite-time " reading. Another important advantage is that, provided we prove that the *cis*- and *trans*-hydroxy-products are formed primarily, simultaneously, and in constant ratio, and that they suffer no subsequent interconversion in the conditions of their formation, we can deduce the steric course of the substitution directly from the proportions in which the hydroxy-isomers are present at the completion of the process, without needing to trace their proportions throughout the reaction. It happens that, on account of the character of the spectra concerned, the latter method would have been difficult to apply.

In following kinetics by the spectrophotometric method, the reaction in alkaline solution is stopped by the addition to withdrawn samples of excess of acid, which also protonates the hydroxyammino-products, to give aquoammino-products. The resulting spectrum thus depends on three coloured substances, the original *trans*-chloroammino-cation and the produced *cis*- and *trans*-aquo-cations. The " infinite-time " samples were also examined after acidification: their spectra depended only on the *cis*- and *trans*-aquo-cations.

Certain questions of stability required to be investigated. By means of spectrophotometric measurements with pure *trans*-chloroammino-salts and pure *cis*- and *trans*-aquoammino-salts, prepared as described in Section 7, it was established (*a*) that the *cis*- and the *trans*-hydroxy-cations in alkaline solution undergo no isomerisation or other reaction at the temperature at which the chlorine displacement was conducted; (*b*) that no isomeric change accompanies the protonation of either hydroxy-cation by acidification to give the corresponding aquo-cation; (*c*) that the *trans*-chloro-cation is stable in acid solution at the temperature of the optical measurements; and (*d*) that the pure *cis*- and *trans*-aquo-cations both remain unchanged in acid solution under the conditions of the analytical measurements. On the other hand, in aqueous acid at higher temperatures than those used in the study of the alkaline hydroxylation, the *trans*-chloro-cation undergoes aquation, as will be described in Section 5.

(1.2) *Kinetics.*—The spectrophotometric method was used, water being the solvent; and the spectra on which it depends are shown in Fig. 1. They have the peculiarity that the absorption curves of the chloro-cation and the two aquo-cations do not differ strongly throughout the visible and near-ultraviolet regions, until near 3000 Å, at which the chloro-cation suddenly becomes strongly absorbing, and both aquo-cations weakly absorbing. At this wavelength then, we can conveniently follow the progress of the hydroxylation,

[1] Werner, *Ber.*, 1911, **44**, 1887.

without concerning ourselves with the stereoisomeric composition of the hydroxy-products, which can have no appreciable influence on the measurements.

It is necessary to be particularly careful about the applicability of Beer's law when working at a wavelength near 3000 Å, because this is not very far from where some of the anions used show appreciable absorption, and near-lying absorption bands of cations and anions are liable to be mutually broadened by the electrostatic interaction of the ions. This upsets Beer's law, because the extent of such interaction depends on concentration. An examination showed that the disturbance was actually inappreciable for the *trans*-chloroammino-salts throughout the range of concentrations over which we used them, but that it began to be appreciable for the *cis*- and *trans*-aquoammino-salts in the concentrations in which they were built up towards the end of some of our runs. If the effect is indeed one of electrostatic interaction, it appears plausible that it should become noticeable at lower concentrations of the triply charged aquo-cations than of the doubly charged chloro-cation. Its influence on the apparent kinetics was to cause a drift in the rate-constants towards the ends of certain runs. That this was an analytical, and not a kinetic, disturbance was

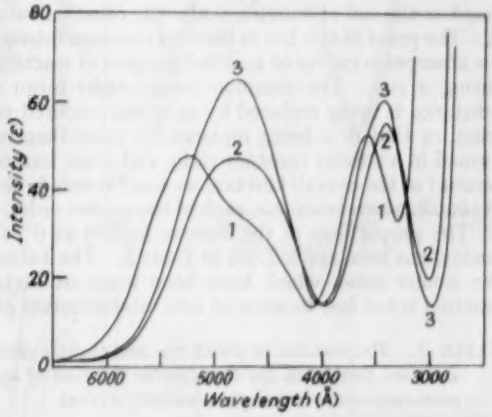

FIG. 1. *Spectrophotometric curves o extinction coefficients for halogeno- and aquo-amminobis(ethylenediamine)-cobalt*(III) *ions in water :*

(1) *trans*-[Co en$_2$(NH$_3$)Cl]$^{2+}$;
(2) *trans*-[Co en$_2$(NH$_3$)(OH$_2$)]$^{3+}$;
(3) *cis*-[Co en$_2$(NH$_3$)(OH$_2$)]$^{3+}$.

confirmed in corresponding experiments with the *cis*-chloroammino-cation, in which it was observed with the spectrophotometric, but not with the titrimetric, method of analysis.

Good second-order rate-constants could be calculated for the major parts of all runs, and for almost the whole of some. It is a result of the doubled charge on the chloro-cation that the negative primary salt effect on reaction rate is noticeable. For ionic strengths up to 0·02, the slope of the plot of the logarithm of the rate constant against the square root of the ionic strength approaches the theoretical slope for point-ions, though at greater ionic strengths the slope falls off, as it should theoretically for space-occupying ions.

Our rate constants, given in Table 1, show this salt effect. The most important thing they show, however, is that, at ionic strengths from 0·02 downwards, these second-order rate constants show only such small variation as is quantitatively required by electrostatic theory, despite a 4-fold variation in the initial concentration of the *trans*-chloro-cation and a 20-fold variation in the initial concentration of hydroxide ion. This leaves no doubt that a bimolecular reaction is under observation.

(1.3) *Steric Course.*—The absorption curves of the chloro- and of the two aquo-cations are ill-adapted for accurate analyses of mixtures of all three coloured materials, because either all three curves, or two of them, follow one another too closely. But the solution at the end of reaction contains no chloro-cation, and, being stable under the conditions of measurement, it can be analysed, after acidification, for the ratio in which the two aquo-cations are present, by using the wavelength at which these cations have the greatest difference of absorption, *viz.*, 4800 Å.

It is then necessary to show that the ratio in which the stereoisomeric products are

TABLE 1. *Spectrophotometric second-order rate-constants for the substitution of hydroxyl for chlorine by hydroxide-ion attack on* trans-*chloroamminobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

[The complex cobalt cation was supplied as its chloride perchlorate, and the hydroxide ion as sodium hydroxide. In some experiments sodium perchlorate was added in order further to raise the ionic strength. The indicator of reaction progress was the optical density of acidified samples at 3000 Å. Initial and final extinction coefficients were taken as $\varepsilon_0 = 312{\cdot}4$ and $\varepsilon_\infty = 13{\cdot}0$. Rate constants were calculated with the equation $k_2 = \{2{\cdot}303/t(b-a)\} \log_{10}\{a(b-x)/(b(a-x)\}$ sec.$^{-1}$ mole^{-1} l.]

Run no.	Initial concns. (mmole/l.) [Co salt]	[NaOH]	Ionic strength	k_2	Run no.	Initial concns. (mmole/l.) [Co salt]	[NaOH]	[$NaClO_4$]	Ionic strength	k_2
11	1·52	0·55	0·0051	1·43	26	1·66	16·04	—	0·0210	1·05
4	0·94	4·17	0·0070	1·22	30	3·35	11·80	—	0·0219	1·03
24	1·66	4·03	0·0091	1·19	31	5·59	11·80	—	0·0286	1·00
25	1·64	7·96	0·0129	1·20	32	8·36	11·80	—	0·0369	0·94
28	0·84	11·80	0·0143	1·18	42	2·77	12·12	20	0·0404	0·79
29	1·65	11·80	0·0168	1·10	41	2·79	12·12	40	0·0605	0·73
44	2·80	12·12	0·0205	1·10						

found at the end of reaction is also the constant ratio in which they appear in the course of it. The proof of this lies in the four common intersections of the curves in Fig. 2, which are the absorption curves of acidified samples of reaction solution, withdrawn at different times during a run. The common intersections mean either that the one original coloured substance is being replaced by only one coloured product (and we know that this is not true), or that it is being replaced by more than one, under the condition that these are formed in a strictly constant ratio, and, once formed, undergo no further change. Taking account of the overall kinetics, we must conclude that the two hydroxy-isomers are formed in simultaneous reactions, each of the second order.

The proportions of the isomers formed at 0°, the only temperature for which kinetic control has been applied, are in Table 2. The Table includes some similar measurements of the isomer ratio, which have been made at higher temperatures, where, however, the reaction is too fast to allow of rate measurements by our method.

TABLE 2. *Proportions in which* cis- *and* trans-*hydroxyamminobis(ethylenediamine)cobalt*(III) *ions are formed in the bimolecular reaction of hydroxide ions in water with* trans-*chloroamminobis(ethylenediamine)cobalt*(III) *ions.*

[Spectrophotometric measurements were made on acidified samples at 4800 Å. The extinction coefficients of the pure aquo-isomers, as determined for this wavelength, were $\varepsilon_{cis} = 65{\cdot}2$ and $\varepsilon_{trans} = 47{\cdot}7$.]

Temperature	0·0°	10·5°	25·0°
Extinction coefficient	61·0	61·6	62·3
cis-Isomer (%)	76	79	83

(2) *Kinetics and Products of the Reaction of Hydroxide Ion with the* d-cis-*Chloroamminobis(ethylenediamine)cobalt*(III) *Ion in Water:* *

$$OH^- + d\text{-}cis\text{-}[Co\ en_2NH_3Cl]^{2+} \longrightarrow d\text{-}cis\text{-} + l\text{-}cis\text{-} + trans\text{-}[Co\ en_2NH_3(OH)]^{2+} + Cl^-.$$

(2.1) *Basic Chemistry.*—All this is as described for the *trans*-chloro-isomer in Sub-section (1.1), except that here the optically active *cis*-chloro-, *cis*-hydroxy-, and *cis*-aquo-cations are optically stable (as well as being stable in the other ways considered in that Sub-section), under conditions relevant to the determination of the kinetics and steric course of the reaction of hydroxide ion with the chloro-cation.

An assumption is necessary concerning the relative configurations of optically active chloro-, hydroxy-, and aquo-cations. The last two are, of course, related by their mutual interconvertibility without stereo-change: in fact, we examine the hydroxy-cation in the form of its protonated derivative, the aquo-cation. As to the relation between optically

* Concerning the configurational labelling of optically active cobalt ions, pending determination of their absolute configurations, see footnote in Part I (*J.*, 1953, 2675). In the present paper we provisionally label as *d* that enantiomer of *cis*-chloro-, -bromo-, or -aquo-amminobis(ethylenediamine)-cobalt(III) which is dextrorotatory for sodium-D light.

active chloro- and aquo-cations, Mathieu [2] concluded from his study of the circular dichroism of the active absorption bands of these cations, that the isomers which are dextrorotatory towards sodium-D light have corresponding configurations. We have accepted this highly probable conclusion.

(2.2) *Kinetics.*—These have been followed by the spectrophotometric method, and checked by titrimetric, and also, though only roughly, by polarimetric examination.

The absorption curve for the *cis*-chloroammino-cation is contained in Fig. 3: it has to be compared with the curves for the *cis*- and *trans*-aquo-cations, given in Fig. 1. The

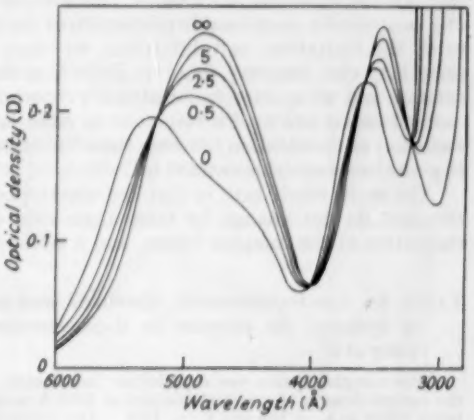

FIG. 2. *Spectrophotometric curves of optical density in a 4-cm. cell of samples from run 3, acidified at various times, given in minutes by the figures associated with the curves. The four common intersections show that the products are being formed in constant proportions.*

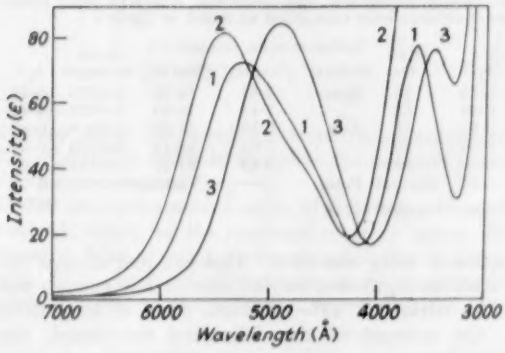

FIG. 3. *Spectrophotometric curves of extinction coefficients for halogeno- and nitrato-amminobis(ethylenediamine)cobalt*(III) *ions in water:*

(1) *cis*-$[Co\ en_2(NH_3)Cl]^{2+}$;
(2) *cis*-$[Co\ en_2(NH_3)Br]^{2+}$;
(3) *cis*-$[Co\ en_2(NH_3)(NO_3)]^{2+}$.

comparison shows that, although, as before, an accurate spectrophotometric determination of the three coloured substances simultaneously in acidified reaction samples is not possible, one can use the optical density at 3000 Å to give the concentration of surviving *cis*-chloro-cation, without needing to know the isomer ratio of the produced aquo-cations; and, at the end of reaction, when the chloro-cation has disappeared, one can use the optical density at 4800 Å to find the ratio of the aquo-isomers. In following the kinetics of the chlorine displacement by means of the optical density of acidified samples at 3000 Å, care was taken to work within the ascertained range of validity of Beer's law, although this meant excluding some readings in the presence of relatively large concentrations of the aquo-cations. Within these wide limits, good second-order rate-constants could be calculated. They are listed in Table 3.

[2] Mathieu, *Bull. Soc. chim. France*, 1936, **3**, 476.

A few runs were followed by measuring the liberated chloride ion in acidified samples by titration with silver nitrate using a silver electrode. As the complex cation was taken in the form of its bromide, the titration curve showed two equivalence points, one in a constant position, corresponding to the end of the precipitation of silver bromide, and a second one in a varying position, representing the completed precipitation of silver chloride: the measurement of chief interest was the separation of these equivalence points. The second-order rate-constants thus obtained are also given in Table 3.

The polarimetric method of following the kinetics was inaccurate, owing to the difficulty of getting enough light, of such wavelength that the rotation underwent sufficient change, through the absorbing solutions. This difficulty was especially great near the beginning of a run, when a considerable proportion of the chloro-cation was present. Having regard to all the limitations and difficulties, we chose to work with sodium-D light. It was of some help that linearity could be proved, as Sub-section (2.3) describes, between optical rotation and the spectrophotometrically determined percentage of reaction. This linearity enabled initial and final rotations to be fixed fairly accurately by extrapolation. For the variation of the rotation between these limits, second-order rate-constants were calculated to give the mean value entered in Table 3.

The main result here is that the spectrophotometric values of the second-order rate-constant do not change by more than 10% over an 8-fold change in the initial concentration of the complex cation, and a 4-fold change in that of the hydroxide ion. It is

TABLE 3. *Spectrophotometric, titrimetric, and polarimetric rate-constants for the substitution of hydroxyl for chlorine in* d-cis-*chloroamminobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

[The complex cation was supplied as its bromide. In the spectrophotometric method of analysis, the optical density of acidified samples at 3000 Å was used, the initial and final extinction coefficients being taken as $\varepsilon_0 = 189$ and $\varepsilon_\infty = 13{\cdot}3$. The titrimetric method employed silver titration of chloride ion. The polarimetric readings were made at 5893 Å, initial and final molecular rotations being taken as $[M]_0 = +525°$ and $[M]_\infty = +157°$. Rate constants were caclulated as noted in Table 1.]

Run no.	Initial concns. (mmole/l.) Method	[Co salt]	[NaOH]	Ionic strength	k_2 *	Run no.	Initial concns. (mmole/l.) Method	[Co salt]	[NaOH]	Ionic strength	k_2 *
14	Spec.	1·76	3·85	0·0091	0·48	19	Spec.	4·51	14·29	0·0278	0·43
16	,,	1·83	7·74	0·0132	0·50	23	,,	7·11	10·87	0·0322	0·45
20	,,	0·90	10·84	0·0135	0·47	35	Titr.	6·38	11·87	0·0310	0·49
17	,,	2·97	7·74	0·0166	0·50	40	,,	7·61	12·12	0·0350	0·52
18	,,	1·86	14·29	0·0199	0·50	36	,,	9·43	11·87	0·0402	0·50
22	,,	3·70	10·87	0·0220	0·47	Several	Polar.	(——— Various ———)			~0·5 (mean)

* In sec.$^{-1}$ mole^{-1} l.

therefore clear that a second-order reaction is being observed. One can just discern the expected negative salt effect, but the ionic strength was carried neither low enough nor high enough to establish it clearly. The titrimetric rate-constants seem to be a little higher than the spectrophotometric. On account of the difficulties mentioned, the polarimetric value is only rough.

(2.3) *Steric Course.*—The ratio in which the alkaline hydrolysis of the *d-cis*-chloro-ammino-cation produces *cis*- and *trans*-hydroxy-cations was determined essentially as described in Sub-section (1.2): it was first shown that the *cis*- and *trans*-aquo-cations appear in a constant ratio on acidification of samples taken at various stages of the reaction; and then the value of that ratio was determined in acidified samples, taken after completion of the reaction, as can then be done by measurement of optical density at 4800 Å.

The new feature of the experiments now described is the determination of the ratio in which the original *d-cis*-chloro-cation produces *d-cis*- and *l-cis*-hydroxy-cations. The type of procedure was broadly similar. It was necessary to show that the enantiomers are produced in a constant ratio, and that, once produced, they suffer no further change: then, the ratio in which they are formed could be equated to the ratio in which they finally appear.

The constancy of the ratio of the formed enantiomers was established by measuring, in a series of acidified examples taken at various times during the progress of reaction, (*a*) the optical density at 3000 Å and (*b*) the optical rotatory power at 5893 Å. The first measurement gave the proportion in which reaction had occurred at the time of sampling, and so the second measurement enabled a relation to be set up between the molecular rotatory power of total complex cations in the acidified solution, and the extent of reaction. This relation proved to be linear, as shown in Fig. 4; and the linearity shows that the *d-cis-* and *l-cis*-hydroxy-cations are appearing in a constant ratio. Their optical stability, once formed, was established by measuring the optical rotatory power at 5893 Å of a series of acidified samples, taken during reaction and long after it had been completed. It was found that the rotatory power changed while reaction continued, but then remained constant for at least 50 half-lives.

The straight line of Fig. 4 can be extrapolated to $[M]_D = +157°$ at 100% reaction. It follows that the *d-cis-*, *l-cis-*, and *trans*-aquo-isomers are then present in such proportions that collectively they have this molecular rotatory power. We may also conclude that, throughout reaction, the *d-cis-*, *l-cis-*, and *trans*-hydroxy-isomers are produced in just the same, constant, proportions. We know the proportion of *trans*-isomer in these isomer

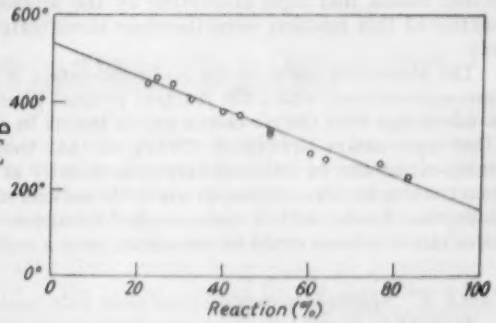

FIG. 4. *Change of rotatory power for* Na-D *light of acidified samples withdrawn at intervals during the reaction of* d-cis-*chloroamminobis(ethylenediamine)cobalt*(III) *ion with hydroxide ion in water at* 0°.

mixtures from the spectrophotometric measurements at 4800 Å. Thus the only figure still required in order to complete the analysis is the molecular rotatory power of a pure *cis*-aquo-enantiomer.

The *cis*-aquo-ammino-series of salts has not yet been optically resolved, and the best available figure for the maximal rotatory power of this cation is due to Mathieu.[2] He prepared it by allowing an aqueous solution of three equivalents of silver nitrate to react with fully resolved *d-cis*-bromoamminobis(ethylenediamine)cobalt(III) bromide. The rotation of the resulting solution was equivalent to $[M]_D$ +450°. A study of the circular

TABLE 4. *Proportions in which* d-cis-, l-cis-, *and* trans-*hydroxyamminobis(ethylenediamine)cobalt*(III) *ions are formed in the bimolecular reaction of hydroxide ions with* d-cis-*chloroamminobis(ethylenediamine)cobalt*(III) *ions in water at* 0°.

	ϵ_{4800}		$[M]_D$
cis-Aquo-cation	65·2	*d-cis*-Aquo-cation	+450°
trans- ,, ...	47·7	Aquo-cation mixture	+157°
Aquo-cation mixture	62·4		

Formed hydroxy-isomers ≡ Final aquo-isomers = { *d-cis* ..... 59·5%; *l-cis* ..... 24·5%; *trans*- ..... 16% }

dichroism of this solution led to the conclusion that the configuration of the aquo-cation corresponded to that of the bromo-cation from which it had been derived, and, furthermore, that little if any racemisation accompanied the aquation. We therefore use this figure in order to complete the isomer analysis, as shown in Table 4.

(3) *Kinetics and Products of the Reaction of Hydroxide Ion with the* d- *and* l-cis-*Bromoamminobis(ethylenediamine)cobalt*(III) *Ions in Water:*

$$OH^- + d\text{- or } l\text{-cis-}[Co\,en_2NH_3Br]^+ \longrightarrow d\text{-cis-} + l\text{-cis-} + trans\text{-}[Co\,en_2NH_3(OH)]^{2+} + Br^-$$

(3.1) *Basic Chemistry.*—The *trans*- and *d*- and *l*-*cis*-series of bromoamminobis(ethylenediamine)cobalt(III) salts are all well characterised: we had available both enantiomeric forms of the *cis*-salts.[1] The same questions of stability were checked as are mentioned in Sub-sections (1.1) and (2.1), by the same methods, and with the same results.

In order to be able fully to specify the steric course of the reaction, we have to make an assumption as to the configurational relation between a bromoammino-cation and an aquoammino-cation having signs of rotation related in a given way. Again we accept Mathieu's conclusion,[2] based on his study of circular dichroism in these materials, that those bromo- and aquo-cations which have the same sign of rotation for sodium-D light have corresponding configurations.

(3.2) *Kinetics.*—The reaction is very fast, and therefore, to give time for sampling, reactant concentrations had to be kept so low as to render inaccurate the titrimetric and the polarimetric method of following the kinetics. The latter method was excluded for the further reason that light absorption by the bromo-cation is inconveniently great. The kinetics of this reaction were therefore investigated by the spectrophotometric method only.

The absorption curve of the *cis*-bromo-cation is in Fig. 3, whilst those of the *cis*- and *trans*-aquo-cations, which the reaction product gives on acidification, are in Fig. 1. It is an advantage that the *cis*-bromo-cation begins to absorb light much more strongly than either aquo-cation already at 3700 Å, so that the kinetics of the disappearance of the bromo-cation can be followed very conveniently at 3400 Å, which is sufficiently removed from the shorter-wave region, in which the cations and anions begin to perturb each other's absorption bands, with a consequential breakdown of Beer's law. Thus, good second-order rate-constants could be calculated, over a sufficient range of reactant concentrations

TABLE 5. *Spectrophotometric second-order rate-constants for the substitution of hydroxyl for bromine in* d- *and* l-cis-*bromoamminobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

[Both enantiomeric bromo-cations were supplied as their bromides. Optical densities of acidified samples at 3400 Å were measured, the initial and final extinction coefficients being taken as $\varepsilon_0 = 405$ and $\varepsilon_\infty = 57{\cdot}3$. Rate constants were calculated as in Table 1.]

Run no.	Initial confign.	Initial concns. (mmole/l.) [Co salt]	[NaOH]	k_2 *		Run no.	Initial confign.	Initial concns. (mmole/l.) [Co salt]	[NaOH]	k_2 *	
110	*d*-	0·73	1·43	3·22	3·26	111	*l*-	0·72	1·43	3·25	3·38
112	,,	1·33	5·49	3·40		113	,,	1·39	5·49	3·55	
114	,,	1·55	9·30	3·29		115	,,	1·55	9·30	3·51	
108	,,	1·61	2·96	3·15		109	,,	1·65	2·95	3·22	

* In sec.$^{-1}$ mole^{-1} l.

TABLE 6. *Proportions in which* d-cis-, l-cis-, *and* trans-*hydroxyamminobis(ethylenediamine)cobalt*(III) *ions are formed in the bimolecular reaction of hydroxide ions with* d-cis- *and with* l-cis-*bromoamminobis(ethylenediamine)cobalt*(III) *ion in water at* 0°.

	ε_{4800}	$[M]_D$
d- or *l*-*cis*-Aquo-cation	65·2	± 450°
trans-Aquo-cation	47·7	—
Aquo-cation mixture from *d*-*cis*-bromo-cation	62·5	+149
,, ,, *l*-*cis* ,,	62·6	−141

From *d*-*cis*-bromo-cation { Formed hydroxy-isomers = final aquo-isomers } = { *d*-*cis* 59%; *l*-*cis* 26%; *trans* 15% }

From *l*-*cis*-bromo-cation { Formed hydroxy-isomers = final aquo-isomers } = { *d*-*cis* 27%; *l*-*cis* 58%; *trans* 15% }

to establish the second-order form of the reaction. Such measurements, some on *d-cis*- and some on *l-cis*-bromo-salts, are recorded in Table 5.

(3.3) *Steric Course.*—The method followed closely the lines sketched in Sub-section (2.3). The results are in Table 6.

(4) *Products of the Reaction of Hydroxide Ion with* dl-cis-*Nitratoamminobis(ethylenediamine)cobalt*(III) *Ion in Water.*

The reaction of this cation with hydroxide ion at 0° in water was too fast to permit kinetic investigation. Thus we have no proof of mechanism, but the high rate itself is an argument in favour of the bimolecular nature of the substitution process.

In the circumstances, we were able to determine only the isomer ratio in the hydroxy-cations formed when the *cis*-nitrato-cation, supplied as nitrate, interacts with sodium hydroxide in water at 0°. The analysis was made, as usual, by measurement of the extinction coefficient at 4800 Å, of the acidified product of the completed reaction. The mean value obtained was 62·8. The composition of the formed hydroxy-substitution product is therefore: *cis* = 86%, *trans* = 14%.

The absorption curve of the *cis*-nitrato-cation was useful in the experiments described in the next Section, and is shown in Fig. 3.

(5) *Rate and Equilibrium in the Aquation of* trans-*Chloro-*, cis-*Chloro-*, cis-*Bromo-, and* cis-*Nitrato-amminobis(ethylenediamine)cobalt*(III) *Ions.*

Examination (pp. 1708, 1710, 1714) of the stabilities of the above cations in acidified aqueous solution at temperatures near those at which their alkaline hydrolysis was investigated showed that no changes occurred in these conditions; but these experiments led us to observe that in acid aqueous solution at raised temperatures the cations undergo an aquation, in which the halogeno- and the nitrato-ligand become replaced by a water molecule. We took the opportunity to make approximate measurements of the rate of these changes. We could not measure their steric course, because, as will be explained, that would have required measurements of the isomer ratio of the *cis*- and *trans*-aquo-products near the commencement of reaction, and, as noted already, we have no method of measuring this ratio in the presence of the halogeno-ions. This is equally true for the nitrato-ion.

However, the rates were measured, sometimes with an optically active *cis*-isomer, or with a racemic *cis*-, or a *trans*-salt; and usually by the spectrophotometric, but occasionally by the titrimetric, method. The reactions were found to be approximately of first order, and some rate constants are given in Table 7.

TABLE 7. *First-order rate-constants* (k_1 *in sec.*$^{-1}$), *and equilibrium extent of aquation of halogeno- and nitrato-amminobis(ethylenediamine)cobalt*(III) *cations in* 0·17N-*aqueous perchloric acid.*

Run no.	Method	Initial salt	$[Salt]_0$ (mmole/l.)	Temp.	10^5k_1	Aquo-formed (%)
47	Spec.	*trans*-$[Co\,en_2NH_2Cl]^{2+}Cl^-ClO_4^-$	3·92	62·6°	3·01	83·3
48	,,	,, ,,	2·42	,,	2·90	85·4
1	,,	,, ,,	3·82	89·9	43·1	83·3
5	Titr.	*dl-cis*-$[Co\,en_2NH_2Cl]^{2+}(Br^-)_2$	11·01	62·6	4·08	88·1
45	Spec.	*d-cis*- ,, ,,	5·28	,,	3·80	86·0
46	,,	,, ,,	4·12	,,	3·97	86·0
119	Spec.	*l-cis*-$[Co\,en_2NH_2Br]^{2+}(Br^-)_2$	3·98	44·8	1·60	92·2
120	,,	,, ,,	1·84	,,	1·76	96·1
117	,,	,, ,,	3·64	62·6	11·6	96·2
118	,,	,, ,,	1·90	,,	12·0	97·7
102	Titr.	*dl-cis*- ,, ,,	8·74	,,	12·0	92·2
	Spec.	,, ,,	,,	,,	13·1	90·1
103	Titr.	,, ,,	10·86	,,	12·5	93·3
203	Spec.	*dl-cis*-$[Co\,en_2NH_2NO_3]^{2+}(NO_3^-)_2$	5·29	44·8	11·2	97
204	,,	,, ,,	3·06	,,	11·1	98
201	,,	,, ,,	3·45	62·6	84·5	99

In their detail, the experimental methods were just as for the investigation of the alkaline reactions of the same halogeno- and nitrato-cations, except, of course, that the samples for analysis had to be chilled and did not require to be acidified. In the spectrophotometric method, the extinction coefficients for completed aquation were taken to be those observed on acidification after the corresponding completed alkaline hydroxylation. Any difference in the isomer ratio of the aquo-cations, as formed by aquation and through alkaline hydrolysis, was thus neglected in the optical calibration; but at the operative wavelengths, 3400 Å in the aquation of the bromo-cation, and 3000 Å in all other cases, the absorption of either aquo-cation is so weak relatively to that of the original halogeno- or nitrato-cation that an uncertainty in the ratio of aquo-isomers makes no practical difference.

It appears that the aquations do not go quite to their stoicheiometric completion: the extents to which the forward reaction was realised are entered in Table 7. One effect of this appreciable reversibility was that, in the absence of an investigation of the kinetics of the retrograde reaction, we had not an exact formula with which to calculate the rate-constants of the forward process. We therefore first calculated a specific rate of approach to equilibrium by means of the formula for a reversible reaction of first order in both directions, and then we multiplied this by the fractional extent to which the aquation goes forward, accepting the resulting first-order rate-constants of the forward process until they began to drift near the equilibrium point. Such drift is an indication that the retrograde reaction is beginning to attain a sufficient relative importance to require a more accurate representation of its kinetic form: but before the onset of drift, the forward rate-constants should be free from error due to an incorrect treatment of the back-reaction.

Another consequence of the reversibility of the aquation is that, whether or not the *cis*- and *trans*-aquo-cations would, at the temperature of the aquations, undergo reversible isomeric change in the absence of disturbance by attacking anions, they are certain to do so, under the influence of the anions present, by the mechanism of reversible anion attack. In some cases more than one kind of anion is present, either from the outset, or at least after anions have been liberated by the aquation; and in these cases parallel attacks, all reversible, by more than one anion could occur. Whether this further complication arises or not, it is clear that the ratio in which the *cis*- and *trans*-aquo-cations are present during aquation will not be constant and equal to the ratio in which they are originally formed, but will drift away from that ratio towards one determined by the thermodynamic situation. Hence the steric course of any of these aquations could be determined only by an extrapolation to zero time of *cis*-*trans* ratios measured at various times near the commencement of reaction; and that, as already explained, is a measurement for which the absorption curves of the substances involved do not provide a method.

It appears from Table 7 that both kinetics and thermodynamics favour aquation in the ligand order $NO_3 > Br > Cl$.

(6) *Summary and Discussion.*

The main results of stereochemical interest reported in the foregoing Sections are brought together in Table 8. Only the reactions of alkaline hydrolysis are included; for the corresponding reactions of aquation were not studied stereochemically, and the kinetic data relating to them are in Table 7.

As noted in previous Parts, there is only partial correlation in these octahedral substitutions between the incidence of stereo-change in the individual molecular acts of substitution and the experimentally observed stereochemical course of the substitutions. The degree of the correlation, optical isomerism being taken into account, is as follows. An initial *trans*-compound, substituted by molecular acts which preserve configuration, will give a *trans*-product, and by molecular acts which involve stereo-change will yield a *cis*-product. An initial *D-cis*-compound, if substituted by molecular processes without stereo-change will yield a *D-cis*-product, but substituted by molecular processes involving stereo-change may give a *trans*-, or an *L-cis*-, or even a *D-cis*-product; and similarly for an initial *L-cis*-compound.

We can therefore translate the experimental results in Table 8 for the *trans*-chloro-cation into molecular terms quite precisely: at 0°, 76% of the molecular acts of substitution involve stereo-change, and 24% do not. As to the *cis*-chloro- and *cis*-bromo-cations, we can say only that at least 40—41% of the molecular processes involve stereo-change, and we cannot say whether any individual transactions occur which lead to

TABLE 8. *Rate and steric course of reactions with hydroxide ion in water of bis(ethylenediamine)cobalt*(III) *ions containing the ammonia ligand.*

d-cis-, *l-cis-*, or *trans*-[Co en$_2$NH$_3$X]$^{2+}$ + OH$^-$ ⟶ *d-cis-*, *l-cis-*, and *trans*-[Co en$_2$NH$_3$(OH)]$^{2+}$ + X$^-$.

(All reactions kinetically of second order.)

Displaced group (X)	Temp.	Rate constant k_2 (sec.$^{-1}$ mole^{-1} l.)	Product ratios (%) *d-cis*	*l-cis*	*trans*
trans-Cl	0·0°	1·25	76		24
,,	10·5	—	79		21
,,	25·0	—	83		17
d-cis-Cl	0·0	0·50	60	24	16
d-cis-Br	,,	3·26	59	26	15
l-cis-Br	,,	3·38	27	58	15
dl-cis-NO_3	,,	—	86		14

substitution with retention of configuration. For the *cis*-nitrato-cation, at least 14% of the molecular acts involve stereo-change, and again we do not know whether any occur which retain configuration.

As to mechanism, there can be no doubt that all the reactions of Table 8 are bimolecular nucleophilic substitutions S_N2.[3] In substitutions at tetrahedral carbon by this mechanism, stereo-change is always complete; and therefore, the most striking result of Table 8 is the evidence it contains that, in substitution at octahedral cobalt by the same mechanism, stereo-change is not complete. The extent to which it is not is known precisely in the case of the *trans*-chloroammino-cation, and, whether the fact is significant or not, it is noticeable that the proportion in which configuration is retained is in the same neighbourhood for this cation as for the *trans*-chloro*iso*thiocyanato- and *trans*-bromo*iso*thiocyanato-cations, the investigation of which is described in the preceding paper. There is also an approximate correspondence between the stereochemical results obtained with the present *cis*-chloro-ammino- and *cis*-bromoammino-cations, and with the *cis*-chloro*iso*thiocyanato-cation of the preceding paper. If the ammino- and *iso*thiocyanato-ligands, $-NH_3^+$ and $-N{:}C{:}S$, have any considerable orienting effects on substitution, it is remarkable that such effects should be so similar, considering how different the ligands are with respect to both formal charge and unsaturation. For the present, these comparisons have their main significance as an incentive to examine other ligands, with a view to determining whether orienting effects are important in octahedral substitutions by the S_N2 mechanism.

There is a certain indication in the data of the preceding paper and of this one that the type of orientation found in bimolecular substitutions by hydroxide ions in octahedral complexes is not fundamentally altered when the displaced group is changed within the range examined, comprising chloro-, bromo-, and nitrato-groups. The invariance suggested is, of course, only an indication, again one requiring further experimental pursuit.

(7) *Preparations.*

trans-Chloroamminobis(ethylenediamine)cobalt(III) chloride perchlorate was prepared by decomposition of *trans*-chloro*iso*thiocyanatobis(ethylenediamine)cobalt(III) perchlorate with 30% hydrogen peroxide, as Werner describes,[4] except for a difference in method of isolation. After reaction, the mixture was evaporated with concentrated hydrochloric acid, and some green crystals of *trans*-dichlorobis(ethylenediamine)cobalt(III) perchlorate, which separated first, were removed. At a later stage red crystals of the desired chloride perchlorate of the

[3] Cf. Part IV, preceding paper.
[4] Werner, *Annalen*, 1912, **386**, 1.

trans-chloro-ammine series separated and were collected. They were recrystallised once from concentrated hydrochloric acid with addition of ethyl alcohol, and then twice from water with added alcohol (Found : C, 13·1; H, 5·2. Calc. for $C_4H_{19}O_4N_5Cl_2Co$: C, 13·1; H, 5·2%). If the last two crystallisations are omitted the salt contains an extra molecule of hydrogen chloride.

cis-Chloroamminobis(ethylenediamine)cobalt(III) salts were prepared from *trans*-dichlorobis(ethylenediamine)cobalt(III) chloride and aqueous ammonia, and the bromide was isolated first and was then converted into the (+)-α-bromocamphor-π-sulphonate for optical resolution, all as described by Werner.[1] From the less soluble diastereoisomer, *d-cis*-chloroamminobis(ethylenediamine)cobalt(III) bromide was obtained, with the aid of concentrated aqueous hydrobromic acid. It was crystallised from warm water with addition of ethyl alcohol (Found : Br, 40·8. Calc. for $C_4H_{19}O_5ClBr_2Co$: Br, 40·7%).

cis-Bromoamminobis(ethylenediamine)cobalt(III) bromide was prepared from diaquotetrahydroxybis(ethylenediamine)cobalt(II)-dicobalt(III) sulphate[5] and ammonium bromide as described by Werner,[4] and was resolved by Werner's method[1] by way of the (+)-α-bromocamphor-π-sulphonates. The less soluble of these, on treatment with concentrated hydrobromic acid, gave *d*-bromoamminobis(ethylenediamine)cobalt(III) bromide (Found : C, 11·2; H, 4·7; N, 16·1; ionic Br, 36·8; total Br, 53·6. Calc. for $C_4H_{19}N_5Br_2Co$: C, 11·0; H, 4·4; N, 16·1; ionic Br, 36·7; total Br, 55·0%). The solution containing the more soluble (+)-α-bromocamphor-π-sulphonate was then fractionally precipitated with sodium dithionate. At first, the racemic dithionate separated, and was removed, but later the optically active dithionate crystallised; and this was converted with concentrated hydrobromic acid into *l*-bromoamminobis(ethylenediamine)cobalt(III) bromide, which was recrystallised from aqueous hydrobromic acid (Found : C, 11·6; H, 4·5; N, 16·1; ionic Br, 36·7%).

The isomeric aquoamminobis(ethylenediamine)cobalt(III) salts were produced together by the action of concentrated aqueous lithium hydroxide on *cis*-bromoamminobis(ethylenediamine)cobalt(III) bromide, much as Werner described for the analogous experiment using potassium hydroxide.[4] The bromides were fractionally crystallised from aqueous hydrobromic acid, the process being followed by means of the absorption spectrum. *trans*-Aquoamminobis(ethylenediamine)cobalt(III) bromide separated first as its monohydrate, and was finally purified by crystallisation to constant absorption spectrum from water with additions of ethyl alcohol (Found : Br, 50·9. Calc. for $C_4H_{23}O_3N_5Br_2Co$: Br, 50·8%). It was converted into the corresponding nitrate by treatment with nitric acid (Found : C, 11·6; H, 5·1. Calc. for $C_4H_{21}O_{10}N_6Co$: C, 12·0; H, 5·3%). The *cis*-aquoamminobis(ethylenediamine)cobalt(III) bromide was obtained from the more soluble fractions in the hydrobromic acid crystallisations, and was crystallised to constant spectrum from aqueous ethyl alcohol (Found : Br, 51·0%). It also was converted into the nitrate. An attempt was made optically to resolve it through the α-bromocamphor-π-sulphonates, but these proved to be too soluble.

cis-Nitratoamminobis(ethylenediamine)cobalt(III) nitrate was prepared by evaporating *cis*-aquoamminobis(ethylenediamine)cobalt(III) nitrate with concentrated nitric acid according to Werner's description.[4] The product was crystallised from aqueous ethyl alcohol until its absorption spectrum was constant, but analysis by combustion was frustrated by the violence of pyrolysis of the salt.

(8) *Methods of Measurement.*

The methods of starting and stopping kinetic runs, both of alkaline hydrolysis, and of aquation, were generally as described in the preceding paper, as also was the technique of analysis by absorption spectrophotometry.

Titrimetric analysis was now concerned with halide-ion content, rather than pH, and, in preparation for these determinations, reaction samples were run into dilute nitric acid. They were titrated electrometrically, a silver wire electrode, the usual agar–salt bridge and calomel half-cell being used.

Reaction samples were prepared for polarimetric measurement exactly as for spectrophotometric.

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[5] Werner and Jantsch, *Ber.*, 1907, **40**, 4430.

337. *Aryl-2-halogenoalkylamines. Part XVII.* The Ultraviolet Absorption Spectra of Some 4-Di-(2-chloroethyl)aminoazobenzenes in Neutral and Acidic Ethanol Solutions.*

By W. C. J. Ross and G. P. Warwick.

The absorption spectra of some substituted 4-di-(2-chloroethyl)aminoazobenzenes and related compounds in neutral and in acidic ethanol solutions have been studied. The absorption spectra of certain 2′-carboxy-derivatives which present unusual features have also been examined in chloroform and in alkaline ethanol solution. Neutral solutions of these acids are considered to contain appreciable proportions of a hydrogen-bonded hybrid (II*a* ⟷ *c* ⟷ *d*).

During studies of cytotoxic chloroethylamino-derivatives of azobenzene an attempt has been made to correlate various chemical and physical properties with biological activities. The measurement of the ultraviolet absorption spectra of a number of derivatives became of interest, first, because of a possible relation between the effects of substituents on the position of absorption maxima and on the biological activity and, secondly, because methods for assessing the reducibility of the azo-linkage in the compounds demanded a knowledge of their absorption characteristics in neutral and acidic solutions.[1]

Absorption Spectra in Neutral Ethanol Solution.—Azobenzenes exhibit weak absorption bands in the regions 210—290 and 440—470 mμ (*R*-band), due respectively to the aromatic ring system and to the –N:N– linkage, and a strong band at about 320—370 mμ (*K*-band) ascribed to the conjugation between the azo-group and the aromatic ring system.[2] Our compounds exhibit the low-intensity band at about 270 mμ and a broad band of high

Table 1. *Absorption spectra of some substituted 4-di-(2-chloroethyl)aminoazobenzenes and related compounds in 95% aqueous ethanol.*

Subst. (I; R = R′ = CH_2·CH_2Cl)	$\lambda_{max.}$ (mμ)	ε	Subst. (I; R = R′ = CH_2·CH_2Cl)	$\lambda_{max.}$ (mμ)	ε
None	397	25,700	4′-SO_2H	405	33,300
2′-Me	395	27,750	2 : 2′-$(MeO)_2$	405—415	25,600
3′-Me	395	26,900	2′-CO_2H, 2-MeO	450—460	33,100
4′-Me	395	29,300	2′-CO_2H, 2-Me	430—450	14,500
2′-Ph	400	26,500		485	17,590
4′-Ph	400—410	40,500	2′-CO_2H, 2 : 4′-Me_2	480—490	28,000
2-MeO	405	29,000	4′-CO_2H, 2-Me	420	28,100
3′-Cl	406	31,400	4′-CO_2H, 3-MeO	420	22,100
4′-Cl	405	31,600	2′-OH, 5′-NO_2	485—490	34,560
4′-Br	405	33,000	2-CO_2H, 4′-NO_2	444	29,000
2′-I	410—415	31,850	(I; R = R′ = Me)		
2′-CO_2H	410—430	19,150	None	410	27,800
	470	20,300	2′-CO_2H	498	32,200
3′-CO_2H	402	30,550	2′-NH_2	440—460	21,480
4′-CO_2H	412	32,300	(I; R = Me, R′ = CH_2·CH_2Cl)		
4′-Ac	435	34,100			
2′-NO_2	420	27,900	2′-CO_2H	415—445	20,650
3′-NO_2	416	30,800		485	24,500
4′-NO_2	446	21,300	2-Carboxyazobenzene	315	12,100
2′-SO_3H	400	27,400			

intensity in the region 390—430 mμ; the latter is apparently a composite of the *R*-band and of the *K*-band which has undergone a bathochromic shift due to the *p*-alkylamino-substituent. Interest has centred on this intense band and the data obtained are shown in Table 1.

The position of the absorption maximum is strongly displaced bathochromically by 2′-, 3′-, and 4′-nitro-groups and by a 4′-acetyl group; the effect from the 4′-position is

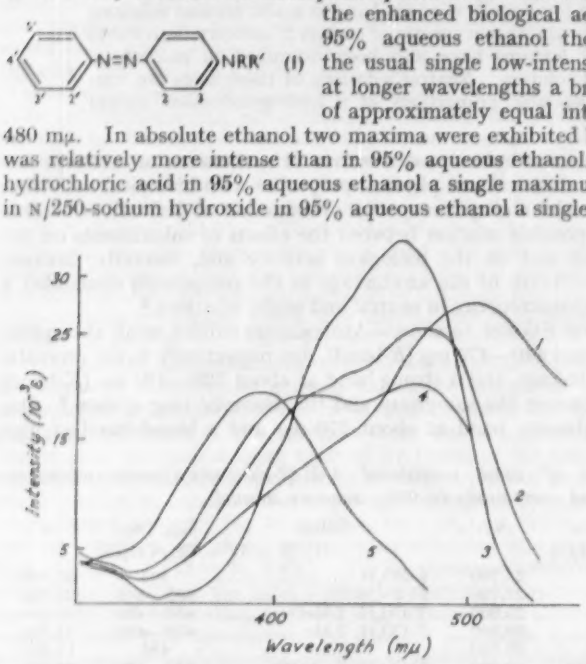
* Part XVI, *J.*, 1956, 1364.

[1] Ross and Warwick, following paper.

[2] Burawoy, *J.*, 1935, 1865; Morton, "Practical Aspects of Absorption Spectrophotometry," *Inst. Chem. Monograph*, 1938, p. 33; Badger and Buttery, *J.*, 1953, 2156.

especially marked. A 4′-phenyl group, a 2-methoxy-group, 2′-, 3′-, and 4′-halogeno-groups, 2′-, 3′, and 4′-carboxy-groups, and 2′- and 4′-sulphonic groups all cause small bathochromic shifts, whilst 2′-, 3′-, and 4′-methyl groups are without significant effect. Substitution of methyl groups in butter yellow (I; R = R′ = Me) by 2-chloroethyl groups causes a hypsochromic displacement.

Introduction of a 2′-carboxy-substituent into the structure (I; R = R′ = $CH_2 \cdot CH_2Cl$) considerably modified the absorption spectrum and this was of especial interest in view of the enhanced biological activity of the compounds. In 95% aqueous ethanol the 2′-carboxy-derivative shows the usual single low-intensity maximum at 270 mμ but at longer wavelengths a broad band having two maxima of approximately equal intensity at 410—430 and 470—480 mμ. In absolute ethanol two maxima were exhibited but the peak at about 470 mμ was relatively more intense than in 95% aqueous ethanol. In chloroform and in N/250-hydrochloric acid in 95% aqueous ethanol a single maximum at 465 mμ was shown while in N/250-sodium hydroxide in 95% aqueous ethanol a single maximum at 395 mμ appeared.



Absorption spectra of 4-di-(2-chloroethyl)aminoazobenzene-2′-carboxylic acid in various solvents.

1, *In* N/2-*ethanolic* HCl.
2, *In* N/250-*ethanolic* HCl.
3, *In pure* $CHCl_3$.
4, *In* 95% *aq.* EtOH.
5, *In* N/250-*ethanolic* NaOH.

The spectrum in absolute ethanol was practically identical with curve 2.

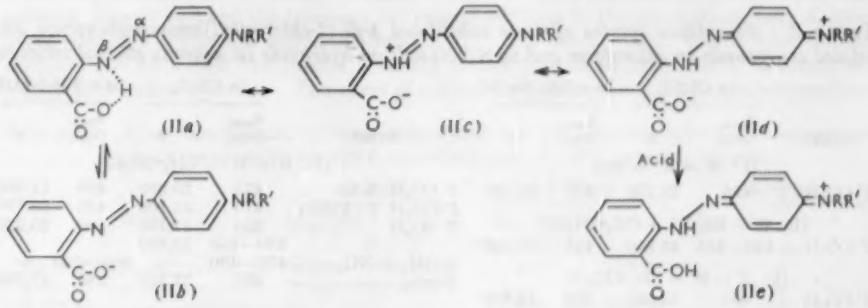
A single maximum was shown at 505 mμ in N/2-hydrochloric acid in 75% aqueous ethanol. These results which were briefly recorded elsewhere [3] are shown in the Figure.

The 3′- and the 4′-carboxy-derivative and the methyl ester of the 2′-carboxy-compound do not show this anomalous absorption which appears to require the presence of an ionisable 2′-carboxyl group. Dr. S. F. D. Orr of this Institute has examined the infrared spectra of several derivatives and has drawn the following conclusions. Carboxylic acids are known to form stable dimers, which are only partially dissociated even in dilute solutions or in the vapour phase at low temperatures. Thus benzoic acid in carbon tetrachloride solution (0·05%) absorbs at 1743 and 3536 $cm.^{-1}$ owing to the CO and OH groups of the monomeric forms and also at 1696 and around 2600 $cm.^{-1}$ owing to hydrogen-bonded CO and OH groups of the dimers; in the solid state, there are only associated forms and absorption is at 1685 and 2500—2700 $cm.^{-1}$. The 3′-carboxy-derivative of the present series behaves in an analogous manner; absorption is found in CCl_4 solution at 1746 and 3537 $cm.^{-1}$, and at 1696 and 2500—2700 $cm.^{-1}$, owing to the monomeric and the dimeric form respectively, while the latter gives rise to absorption in the solid state at 1688 and around 2600 $cm.^{-1}$. With the 2′-carboxy-compound, however, in dilute CCl_4 solution, bands at 1746 and 2785 $cm.^{-1}$ are observed, and in the solid state at 1730 and about 2750 $cm.^{-1}$; these results mean that the carbonyl group is free but the hydroxyl group is associated under all conditions; this is possible only if an intramolecular hydrogen bond is formed between the hydroxyl group and the azo-nitrogen atom as postulated below. Methyl-red behaves in the same manner as

[3] Ross and Warwick, *Chem. and Ind.*, 1955, 745; see also Warwick, Thesis, London, 1955.

this 2′-carboxy-compound; the 4′-compound could only be measured in the solid state and was similar to the 3′-compound.

It is considered that solutions of 4-di-(2-chloroethyl)aminoazobenzene-2′-carboxylic acid (II*a*; R = R′ = CH_2·CH_2Cl) contain the species indicated in the annexed scheme. In neutral solution an equilibrium exists between the dissociated form (II*b*) and the undissociated form which is regarded as a resonance hybrid (II*a* ⟷ *c* ⟷ *d*) of a



hydrogen-bonded structure. It seems probable that the quinonoid form (II*d*) is present in the highest proportion since the maximum at 470—480 mμ, now considered to be associated with the hybrid, approaches that of the cationic quinonoid form (II*c*) which is present in strongly acid solutions.

This scheme appears to account for the various changes in spectra which have been observed. Thus in chloroform solution and in weakly acidic solution there will be practically no dissociation and the spectrum is that of the resonance hybrid; in alkaline solution the anionic form (II*b*) predominates; both forms are present in absolute ethanol and in 95% aqueous ethanol and, as would be expected, rather more of the dissociated form is present in the latter solution. A hydrogen-bonded structure for 4-di-(2-chloroethyl)aminoazobenzene-2′-carboxylic acid (II*a*; R = R′ = CH_2·CH_2Cl) and methyl-red [5] (II*a*; R = R′ = Me) is also supported by the greater solubility in chloroform and carbon tetrachloride of the 2′-carboxy-derivative compared with the 3′- and the 4′-isomer. The powerful chelating action of 2′-carboxy-azo-compounds [6] also suggests such bonding in the parent acids.

If hydrogen bonding occurs between the carboxyl group and the β-nitrogen atom of the azo-linkage then modifications to the molecule which would increase the basicity of this nitrogen atom should increase the proportion of the bonded hybrid structure (II*a* ⟷ *c* ⟷ *d*) at the expense of the anionic form (II*b*). This would be due partly to the decreased acidity of the carboxyl group and partly to the increased probability of hydrogen bonding. It now appears to be established that increasing electron-release from the 4-position increases the basicity of the β-nitrogen atom [7] and it has now been shown (Table 1) that the proportion of hydrogen-bonded form in neutral alcoholic solution increases in the order (II*a*; R = R′ = CH_2·CH_2Cl) < (II*a*; R = Et, R′ = CH_3·CH_2Cl) < (II*a*; R = R′ = Me), *i.e.*, in the order of increasing basicity of the β-nitrogen atom. The last-mentioned compound, methyl-red, represents the extreme case in which only the hydrogen-bonded form is present in 95% aqueous ethanol, the position of the absorption maximum in this solvent being identical with that in chloroform (Tables 1 and 2). The introduction of a 2-methyl substituent into (II*a*; R = R′ = CH_2·CH_2Cl) also increases the basicity of the β-nitrogen atom (cf. ref. 7*c*) and the intensity of the maximum at 485 mμ is increased at the expense of the maximum at 430—450 mμ. Further substitution in the

[5] Davies and Sutherland, *J. Chem. Phys.*, 1938, **6**, 755; Flitt, *J.*, 1951, 962.
[6] Cf. Mecke and Schmähl, *Naturwiss.*, 1955, **42**, 153.
[6] Drew and Landquist, *J.*, 1938, 292.
[7] (*a*) Rogers, Campbell, and Maatman, *J. Amer. Chem. Soc.*, 1951, **73**, 5122; (*b*) Badger, Buttery, and Lewis, *J.*, 1954, 1888; (*c*) Sawicki and Ray, *J. Org. Chem.*, 1954, **19**, 1686.

4′-position gives the 2 : 4′-dimethyl-2′-carboxylic acid which resembles methyl-red in showing a single maximum at the longer wavelength.

It is of interest that adding appreciable amounts of water to alcoholic solutions of azo-compounds causes the appearance of a new band bathochromically displaced some 50 mμ from the original intense band : this is ascribed to hydrogen bonding between water molecules and the more basic nitrogen atom of the azo-linkage.[8] The displacement is in the same direction and of the same order of magnitude as that now observed in the case

TABLE 2. *Absorption spectra of some substituted 4-di-(2-chloroethyl)aminoazobenzenes and related compounds in chloroform and in* N/250*-sodium hydroxide in aqueous ethanol solution.*

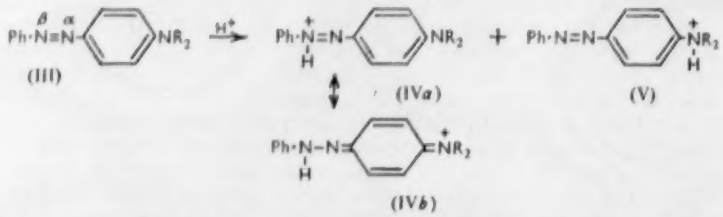
	In $CHCl_3$		In N/250-NaOH	
Subst.	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
(I; R = R′ = Me)				
2′-CO_2H ...	495	39,730	405	21,550
(I; R = Et, R′ = CH_2·CH_2Cl)				
2′-CO_2H ...	480—485	45,800	405	22,200
(I; R = R′ = CH_2·CH_2Cl)				
2′-CO_2H ...	465	34,000	395	19,600

	In $CHCl_3$		In N/250-NaOH	
Subst.	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
(I; R = R′ = CH_2·CH_2Cl)				
2′-CO_2H, 2-Me ...	475	25,900	400	11,900
2′-CO_2H, 2 : 4′-Me_2	475	32,100	400	35,770
2′-SO_3H	555	31,150	400	20,320
	530—540	29,880		
2′-OH, 5′-NO_2	475—490	—	505—520	—
None	395	32,220	385	17,700

of the 2′-carboxy-derivative when compared with the corresponding 3′- and 4′-isomers. The high activity of the 2′-carboxylic acid derivatives as tumour-growth inhibitors may be connected with an ability to form chelate compounds with traces of metals or with the increased lipoid-solubility resulting from a hydrogen-bonded structure, but it seems more likely to be related to the relative ease of reduction of the azo-linkage which is discussed in the following paper.

The 2′-sulphonic acid is a sufficiently strong acid ($pK_a < 3$ in 50% aqueous acetone) for it to exist entirely in the anionic form in 95% aqueous ethanol, a maximum being shown at 400 mμ at the same position as in alkaline solution (Tables 1 and 2). In absolute ethanol a second peak appears at 530 mμ, and in chloroform, in which a hydrogen-bonded structure is presumed to exist, the maximum at 400 mμ is absent.

Absorption Spectra in Acidic Ethanol Solution.—According to Badger, Buttery, and Lewis [7b] it seems probable that the species (III), (IV) are present in moderately acidic solutions of *p*-alkylaminoazobenzenes. Of these (IV*a* and *b*) are extreme forms of a



resonance hybrid which is considered to give rise to a band in the region of 530 mμ (called the *Q*-band), while the tautomeric form (V) is considered responsible for a band which appears at about 320 mμ (called the *K*′-band). The acid concentration (0·5N-hydrochloric acid in 75% aqueous ethanol) used in our measurements was dictated by the requirements of the stannous chloride reduction experiments—the conditions chosen gave conveniently measured rates of reaction and all the compounds which it was desired to examine were then in solution. At this acid concentration the base-strength-reducing effect of the 2-chloroethyl substituents on the amino-nitrogen atom, due to the electron-attracting capacity of the chlorine atoms [9] possibly coupled with steric hindrance, results

[8] Brode, Seldin, Spoerri, and Wyman, *J. Amer. Chem. Soc.*, 1955, **77**, 2762.
[9] Ross, *J.*, 1949, **183**.

in proton addition exclusively at the azo-linkage in all but one example (see below) and no *K'*-bands were detected. Most of the compounds examined were present partly in the uncharged form (giving a *K*-band) and partly as the cation (giving a *Q*-band); the results are shown in Table 3.

As would be expected from their effect on the basicity of the azo-linkage, electron-releasing substituents tended to increase the proportion in the cationic form whilst electron-attracting substituents decreased the proportion. 2'-Substituents, independently of their polarity, greatly reduced the tendency for proton addition to the azo-linkage, only *K*-bands being observed under the conditions employed. This effect, which is well established,[10] supports the view that the proton is added to the β-nitrogen atom, for a 2'-substituent would hinder such addition. The effect of a 2'-carboxy-group and of a 2'-methoxycarbonyl

TABLE 3. *Absorption spectra of some substituted 4-di-(2-chloroethyl)aminoazobenzenes and related compounds in N/2-hydrochloric acid in 75% aqueous ethanol.*

	Q-Band		*K*-Band		*K'*-Band	
Subst.	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	λ_{max} (mμ)	ε
	(I; R = R' = $CH_2{\cdot}CH_2Cl$)					
None	530	22,660	400	19,770	—	—
2-Me	520	46,390	—	—	—	—
2'-Me	—	—	400	27,100	—	—
3'-Me	530	23,340	400	19,130	—	—
4'-Me	530	23,750	400	20,130	—	—
2'-Ph	—	—	400	28,860	—	—
4'-Ph	555	25,220	410—415	24,610	—	—
2-MeO	(480—490	55,310) [a]	—	—	—	—
3'-MeO	530	21,270	400	22,080	—	—
4'-MeO	565	19,830	410	19,950	—	—
2'-Cl	—	—	410	29,610	—	—
3'-Cl	520	9,280	410	29,400	—	—
4'-Cl	530	11,070	400	26,940	—	—
2'-Br	—	—	415	37,360	—	—
3'-Br	515	7,300	410—415	27,930	—	—
4'-Br	530	10,780	410	28,470	—	—
2'-I	—	—	415	29,430	—	—
2'-CO_2H	505	30,200	—	—	—	—
3'-CO_2H	530	9,300	405	26,810	—	—
4'-CO_2H	530	Infl.	425	22,480	—	—
2'-CO_2Me	530	17,510	405	18,930	—	—
4'-Ac	—	—	435	27,760	—	—
2'-SO_3H	550	33,410	405—410	7,200	—	—
	535	34,610				
4'-SO_3H	525	14,940	420	24,850	—	—
2'-CO_2H, 2-Me	530	45,300	—	—	—	—
2'-CO_2H, 2-MeO	500—510	54,800	—	—	—	—
2'-CO_2H, 2 : 4'-Me_2	530—540	46,070	—	—	—	—
4'-CO_2H, 2-Me	530	40,940	—	—	—	—
4'-CO_2H, 3-MeO	515—520	8,980	425—430	14,400	310—315	9,770
Azobenzene	—	—	320	18,400	—	—
	(I; R = R' = Me)					
None	525	34,700	—	—	320	10,940
2'-CO_2H	515	39,900	—	—	325—330	3,980
	(I; R = Et, R' = $CH_2{\cdot}CH_2Cl$)					
2'-CO_2H	525	36,000	—	—	—	—

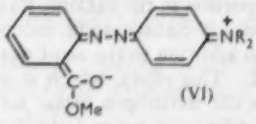
(*a*) For a discussion of the position of this maximum see p. 1724.

group is exceptional. It has already been postulated that the 2'-carboxylic acid exists in neutral solutions in the forms (II*a*—*d*). It would be expected that proton addition could occur quite readily to the unhindered carboxylate ion in forms (II*c* and *d*). Similarly the methyl ester probably exists in a number of forms, including (VI), to which proton addition would proceed without difficulty.

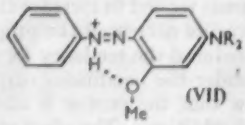
The 2-methoxy-derivative shows a maximum at 480—490 mμ, which is at a considerably

[10] (*a*) Miller, Sapp, and Miller, *J. Amer. Chem. Soc.*, 1948, **70**, 3458; (*b*) Badger and Lewis, *J.*, 1953, 2147; (*c*) Badger and Buttery, *J.*, 1953, 2156.

shorter wavelength than that associated with other quinonoid forms. Since the corresponding 2-methyl derivative shows a normal maximum at 530 mμ it appears that the presence of the oxygen atom is responsible for the hypsochromic displacement of the *Q*-band. It is possible that the form (VII) is stabilised by hydrogen bonding as shown, thus increasing the azo-character of the absorption.



(VI)



(VII)

K'-Bands corresponding to form (V) have been shown in our series only by methyl-red and by 4-di-(2-chloroethyl)amino-3-methoxyazobenzene-2'-carboxylic acid. The presence of this form indicates increased basicity of the amino-group. In the first case this is due to the replacement of the chloroethyl groups by methyl groups and in the second to the steric hindrance to coplanarity of the di-(2-chloroethyl)amino-group with the conjugated system—a similar effect due to a 3-methyl substituent has been recorded.[10a]

Experimental.—The preparation of the substituted *p*-di-(2-chloroethyl)aminoazobenzenes was described in Part XVI.

Ultraviolet absorption spectra were measured at 24° by means of a Unicam Model SP 500 quartz spectrophotometer which had been adapted to have thermostatic control of the cell housing. The concentration of the azo-compound was 10^{-5}M in all cases. N/250-Ethanolic sodium hydroxide (Table 2) was prepared by diluting 4 ml. of 0·1N-aqueous sodium hydroxide to 100 ml. with ethanol, and the N/2-ethanolic hydrochloric acid (Table 3) by diluting 25 ml. of 2N-aqueous acid to 100 ml. with ethanol.

Infrared spectra were measured by using a Perkin-Elmer Model 112 spectrometer, with a rock-salt prism below 2000 cm.$^{-1}$, and one of lithium fluoride above this.

The authors thank Dr. S. F. D. Orr for measuring and interpreting the infrared spectra of the carboxy-derivatives and Dr. G. E. Lewis for helpful discussions.

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338. *Aryl-2-halogenoalkylamines. Part XVIII.* The Rates of Reduction of Substituted 4-Di-(2-chloroethyl)aminoazobenzenes by Stannous Chloride, Hydrazine, and the Xanthine Oxidase–Xanthine System.*

By W. C. J. Ross and G. P. Warwick.

The rates of reduction of thirty-nine 4-di-(2-chloroethyl)aminoazobenzene derivatives by acid stannous chloride and by hydrazine in neutral ethanolic solution have been measured. The effect of substituents on the reducibility of the azo-linkage is discussed; for reduction in acid solution the effect of 3'- and 4'- substituents can be expressed by the Hammett equation, ρ having the value 1·59. The rates of reduction of some water-soluble azo-derivatives by the xanthine oxidase–xanthine system in pyrophosphate buffer under anærobic conditions have also been measured. The results are consistent with the hypothesis that reduction of the azo-linkage potentiates inhibition of tumour growth by the azo-compounds.

In Part XVI * reference was made to the desirability of finding whether the relative rates of reduction of various 4-di-(2-chloroethyl)aminoazobenzenes could be correlated with their biological activities. Such relative rates have been determined by using polarography, catalytic hydrogenation, chemical reagents, and enzyme systems. It has been difficult to interpret the polarographic results particularly since it has not been agreed that the systems

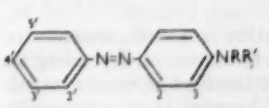
* Parts XVI, XVII, *J.*, 1956, 1364 and preceding paper.

are reversible.[1] It has been stated that " the rate of reaction between an oxidant and a reducing agent is not simply determined by the difference in the oxidation–reduction potential of the two systems. Frequently the chemical nature of the reagent used is of primary importance with regard to the rate of reaction." [2] So we have measured actual rates of reduction. Despite the uncertainties of interpreting the polarographic results and of relating them to biological conditions some tentative conclusions emerge from this earlier work. Shikata and Tachi [3] found the order of reducibility : 4-dimethylamino- < 4-amino-azobenzene < azobenzene. Vladimirstev and Postovski [4] indicate the order : 4-hydroxy- < 4-methoxy- < 4-acetoxy-azobenzene < azobenzene. These results are consistent with Shikata and Tachi's electronegativity rule of reduction potentials,[3] that is, that organic compounds are more easily reduced as more electronegative groups are introduced into the molecule.

The relative rates of catalytic hydrogenation of sulphonamide azo-dyes related to prontosil were measured by Hamon,[5] using a standardised preparation of Raney nickel under controlled conditions of temperature and agitation. There is again considerable difficulty in relating the results to biological systems, for it is known that the relative rate and even the course of hydrogenation can be influenced by a change of catalyst or of solvent. For example, while Hamon [5] found that azobenzene took up two mols. of hydrogen at a steady rate to give aniline under her standard conditions, Skita,[6] using colloidal platinum, found that reduction to hydrazobenzene was rapid and was followed by a further slow reduction. Nevertheless under Hamon's conditions it was shown that in non-basically substituted azobenzenes a 4-methyl substituent hindered reduction whilst a 2-methyl group facilitated it. A 2-carboxy-substituent caused an initial increase in the rate but this decreased before two mols. of hydrogen had been taken up : it was considered that the increased speed of reduction could be attributed to increased electron density at the azo-linkage which resulted from the presence of the 2-substituent.

Tiffeneau [7] showed that, in the reduction of the closely related phenylhydrazine structure by stannous chloride, introduction of one or two methyl groups into the 2- and 4-position of the aromatic ring increased the rate of reaction. Tréfouël and his co-workers [8] measured the rate of reduction of some biologically effective azo-compounds, using cysteine in aqueous solution at 95°, and demonstrated a relation between this rate and activity. Finally, Mecke and Schmähl [9] found that in the enzymic reduction of 4-dimethylaminoazobenzene derivatives by baker's yeast, the introduction of a 2′-hydroxy-substituent reduced the rate of reaction whilst the introduction of a 4′-carboxy-group and especially of a 2′-carboxy-group increased it.

We have used chemical reagents in homogeneous solutions. At first stannous chloride in 0·5N-hydrochloric acid in 75% aqueous ethanol was used, the intensity of the major absorption band (see Part XVII) yielding the concentration of azo-compound. A large excess of stannous chloride was used and, the reaction, being of the first order with respect to azo-compound, exhibited unimolecular kinetics. In order to eliminate errors due to small variations in temperature or in stannous chloride titre, the rate of reduction of the reference compound (I; R = R′ = CH_2·CH_2Cl) was measured simultaneously with that of the compound under test. The unimolecular rate constants are expressed relative to the value for the unsubstituted compound (I; R = R′ = CH_2·CH_2Cl) (Table 1). In all cases the absorption in the region of the *Q*- and *K*-bands fell to an extremely low value at the end of



(I)

[1] Billmann and Blom, *J.*, 1924, **125**, 1719; Conant and Pratt, *J. Amer. Chem. Soc.*, 1926, **48**, 2468; Shikata and Tachi, *Mem. Coll. Agr. Kyoto Imp. Univ.*, 1931, **17**, 45; Tachi, *ibid.*, 1937, **40**, 1, 11; 1938, **42**, 1; Hillson and Birnbaum, *Trans. Faraday Soc.*, 1952, **48**, 478; Page, *Quart. Rev.*, 1952, **6**, 298.
[2] Kolthoff and Lingane, " Polarography," Interscience Publ. Inc., New York, 1946, p. 349.
[3] Shikata and Tachi, *J. Chem. Soc. Japan*, 1932, **53**, 834; *Coll. Czech. Chem. Comm.*, 1938, **10**, 368.
[4] Vladimirstev and Postovskii, *Doklady Akad. Nauk, S.S.S.R.*, 1952, **83**, 855.
[5] Hamon, *Ann. Chim.* (*France*), 1947, **2**, 233.
[6] Skita, *Ber.*, 1912, **45**, 3312.
[7] Tiffeneau and Orekhoff, II Cons. Chim. Inst. Internat. Chim. Solvay, 1926, p. 247.
[8] Tréfouël, Tréfouël, Nitti, Bovet, and Hamon, *Compt. rend. Soc. Biol.*, 1938, **129**, 950.
[9] Mecke and Schmähl, *Naturwiss.*, 1955, **42**, 153.

the reaction and whenever isolation of products was undertaken only amines were obtained.

Table 1 shows that 3′- and 4′-substituents have the effect on the rate of reduction which would have been predicted from the " Electronegativity rule," electron-attracting groups

TABLE 1. *Relative rates of reduction of a series of substituted* 4-*di*-(2-*chloroethyl*)*aminoazobenzenes and related compounds using* (i) *stannous chloride in* 0·5N-*hydrochloric acid in* 75% *aqueous ethanol and* (ii) *hydrazine in* 50% *aqueous ethanol at* pH 8.

Subst.	Rel. rate const. (i)	Rel. rate const. (ii)	Biol. activity [a]
(I; R = R′ = CH_2·CH_2Cl)			
None	100	100	+
2-Me	V. low	359	Low
2′-Me	62	187	Low
3′-Me	94	109	—
4′-Me	36	97	—
2′ : 3′-Benzo	157	204	—
2′-Ph	68	169	—
4′-Ph	101	85	—
2-MeO	152	468	+
3′-MeO	204	122	—
4′-MeO	20	82	—
2′-Cl	113	193	—
3′-Cl	278	107	—
4′-Cl	206	98	—
2′-Br	80	170	—
3′-Br	297	97	—
4′-Br	254	97	—
2′-I	39	189	—
4′-Ac	2100	116	—
2′-CO_2Me	V. high	118	+
2′-CO_2H	V. high	235	+
3′-CO_2H	166	126	—
4′-CO_2H	1180	136	—
2′-NO_2	>1500 [b]	— [c]	—
3′-NO_2	—	85	—
2′-SO_2H	2470	395	—
4′-SO_2H	374	146	—
2′ : 3′-Cl_2	90	195	—
2′ : 4′-Cl_2	75	149	—
3′ : 4′-Cl_2	417	103	—
2′-CO_2H,2-Me	562	519	+
2′-CO_2H,2-MeO	91	617	+
2′-CO_2H,2 : 4′-Me_2	168	512	+
4′-CO_2H,2-Me	93	366	+
(I; R = Et, R′ = CH_2·CH_2Cl)			
2′-CO_2H	2330	159	—
(I; R = R′ = Me)			
None	77	94	—
2′-CO_2H	423	61	—
Azobenzene	316	189	
Azobenzene-2-carboxylic acid	1100	100	

[a] As inhibitors of the growth of the transplanted Walker rat carcinoma. [b] One of the end products in this reaction is *o*-nitroaniline (see p. 1728). [c] The end product in this reaction is a triazole oxide (see p. 1728).

increasing the rate. A plot of Hammett's σ values [10] against the logarithm of the relative rate constant gives a reasonably straight line which indicates a value of 1·59 for ρ in the equation $\log k - \log k_0 = \sigma\rho$. Considerable divergence from the linear relation occurred only with substituents for which Hammett gave a wide range of values for σ (Fig. 1).

In view of the complexity of the reaction which involves the reduction of azo-compounds present in differing proportions of azo- and quinonoid forms (see Table 3, Part XVII) the agreement with the Hammett equation is striking.

The effect of substituents *ortho* to the azo-linkage is, as in other instances, anomalous. A halogen atom in the 2′-position generally hinders reduction, to an extent depending on the size of the atom. For while a 2′-chlorine atom alone has little effect it causes retardation in conjunction with an extra 3′- or 4′-chlorine atom, and a 2′-bromine atom or especially a 2′-iodine atom is rate-reducing. A 2′-phenyl group hinders reduction but a 4′-phenyl group has little influence. 2′-Carboxy- and 2′-methoxycarbonyl groups greatly accelerate the reaction and it is noteworthy that these groups are exceptional in not hindering the addition of a proton to the azo-linkage, an effect observed with most other 2′-substituents (Table 3, Part XVII). It might be considered that this indicates that the quinonoid form of the azo-compound is the more readily reduced but this would not be consistent with the moderate rates of reduction of the 2-methyl-2′- and -4′-acids which are present exclusively in the quinonoid form. The further insertion of a 2-methyl or 2-methoxy-group into the 2′-carboxylic acid reduces the very high rate, the latter substituent being the more

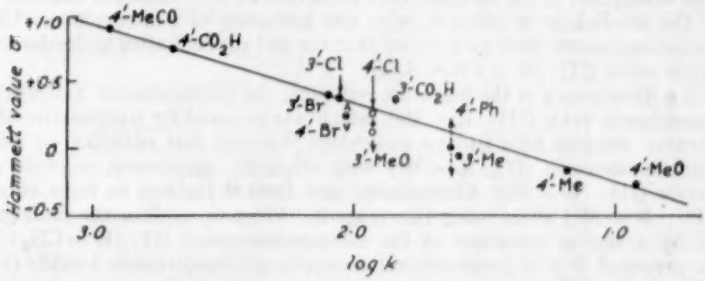
[10] Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, p. 188.

effective although the relative effects of these substituents are reversed in the absence of the 2′-carboxyl group.

A 4-dimethylamino-group reduces the rate of reduction more than does a 4-di-(2-chloroethyl)amino-substituent, in accord with the greater electron-releasing potentiality of the former. It is of interest that the introduction of a 2′-carboxy-group into azobenzene and into 4-dimethylaminoazobenzene has not nearly the same accelerating effect that it has in 4-di-(2-chloroethyl)aminoazobenzene.

It was, of course, realised that the relative order of reducibility of the azo-compounds in acid solution did not necessarily bear any relation to the order under physiological conditions, especially as at pH 7·5 all the compounds would be entirely in the azo-form;

FIG. 1. *Relation between* log *k* *and* σ *for the stannous chloride reaction.* ←·→ *indicates the range of values given by Hammett* [10] *in divergent examples.*



so measurements were also made in nearly neutral solutions. Stannous chloride could not be used under these conditions and at first sodium dithionite was examined. However, stock solutions of this reagent deteriorated rapidly, even under nitrogen, owing to a reaction with water which gave thiosulphate and hydrogen sulphite. The development of acidity made it practically impossible to maintain neutrality during reduction runs since adequate concentrations of buffer salts could not be achieved in the alcohol concentration required to dissolve sufficient azo-compound. The results with this reagent were consequently erratic but the general trend indicated that, regardless of their polarity, 3′- and 4′-substituents had little effect on the rate whereas 2′-substituents facilitated reaction.

The use of thiourea dioxide as a reagent for the reduction of azo-compounds has been reported by Gore [11] but it was found to be unsuitable for our studies. Although the azo-compounds were reduced there was a variable time lag before reaction started, which suggested that the dioxide was being converted into some other compound which was the true reducing agent. This was supported by a fairly rapid change in the absorption spectrum of freshly prepared aqueous-ethanolic solutions of thiourea dioxide.

Eventually a partially neutralised solution of hydrazine dihydrochloride in 50% aqueous ethanol was found to be a suitable reagent. The stock solution was stable and acted as its own buffer at pH 8. By using a large excess of hydrazine, unimolecular kinetics were imposed and, as before, reduction runs with the test substance and 4-di-(2-chloroethyl)-aminoazobenzene were carried out simultaneously. The ratios of the unimolecular rate constants were derived by a graphical method and the results are shown in Table 1.

The Table shows that, in striking contrast to their effect on the stannous choride reduction, 3′- and 4′-substituents have here little effect. The outstanding feature is the accelerating effect of all substituents *ortho* to the azo-linkage in 4-di-(2-chloroethyl)aminoazobenzene. Maximum accelerating effects are produced by 2-methoxy, 2-methyl, and 2′-sulphonic acid groups. Insertion of a 2′-halogen atom approximately doubles the rate of reduction irrespective of the size of the halogen atom (cf. p. 1726). The rate-increasing effect of a 2′-carboxylic acid group is reduced on esterification and it is noteworthy that this acid

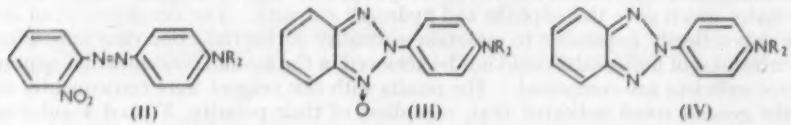
[11] Gore, *Chem. and Ind.*, 1954, 1355.

group hinders reduction when inserted into the azobenzene and 4-dimethylaminoazobenzene structure. There is one feature common to the results of stannous chloride and hydrazine reduction, *viz.*, the rate of reduction of substituted 2′-azobenzenecarboxylic acids is in the order : 4-N(CH_2·CH_2Cl)$_2$ > 4-NEt(CH_2·CH_2Cl) > 4-H > 4-NMe_2.

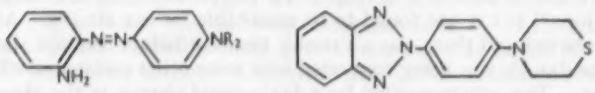
There is evidence that the initial product obtained in the hydrazine reductions is a hydrazo-compound, for in a number of cases re-oxidation with iodine has resulted in increased absorption in the region of the azo-*K*-band. Eventually this property is lost and it appears that fission of the molecule to give amines occurs. Hydrazobenzene can be isolated when azobenzene is treated with hydrazine under the conditions of the reduction experiments, but 4-dialkylaminohydrazobenzenes seem to be too unstable for ready isolation.[12]

The reduction of the 2′-nitro-derivative (II; R = CH_2·CH_2Cl) is potentially complex since either or both the azo-linkage and the nitro-group could be involved. The final steady light absorption of the solution after reduction by acid stannous chloride indicates that only the azo-linkage is affected, with the formation of *o*-nitroaniline. Ultraviolet absorption measurements have now shown that the end product after hydrazine treatment is the triazole oxide (III; R = CH_2·CH_2Cl).

There is a discrepancy in the literature regarding the preparation of 2-dimethylaminophenylbenzotriazole oxide (III; R = Me), which was required for comparative absorption measurements; whereas Elbs and his co-workers [13] stated that reduction of 4-dimethylamino-2′-nitroazobenzene (II; R = Me) with ethanolic ammonium sulphide gave the triazole oxide (III; R = Me), Chakrabarty and Dutt [14] claimed to have obtained the triazole (IV; R = Me) when using this reagent. We now confirm the findings of Elbs *et al.* and by a similar reduction of the nitroazo-compound (II; R = CH_2·CH_2Cl) we have also prepared 2-[*p*-di-(2-chloroethyl)aminophenyl]benzotriazole 1-oxide (III; R = CH_2·CH_2Cl) which exhibits an absorption spectrum similar to that of the dimethylamino-derivative (III; R = Me). Reduction of the triazole oxide (III; R = Me or CH_2·CH_2Cl) with stannous chloride gave the corresponding triazole (IV; R = Me or CH_2·CH_2Cl).



(II) (III) (IV)



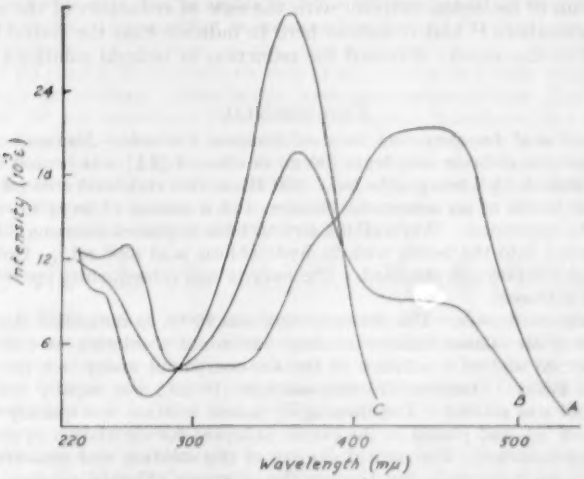
(V) (VI)

Elbs *et al.*[13] also reported that the reduction of the nitroazo-compound (II; R = Me) by ethanolic sodium sulphide gave the aminoazo-derivative (V; R = Me) and this was of interest as an indication of a possible route to the 2′-aminoazobenzene compound (V; R = CH_2·CH_2Cl). On repeating the reduction of the compound (II; R = Me) we obtained an apparently homogeneous product of m. p. 133—134° (Elbs *et al.*[13] gave m. p. 133—134° for their so-called aminoazo-compound). However a solution of the product in benzene showed a strong fluorescence similar to that of the triazole (IV; R = Me) and the ultraviolet absorption was unlike that expected for a compound of structure (V; R = Me) since it contained an intense maximum at 365 mμ and an inflection between 410 and 460 mμ (Fig. 2). Chromatographic resolution on alumina showed that the product was composed of 90% of the triazole (IV; R = Me), m. p. 187°, and 10% of the aminoazo-compound

[12] Cf. Miller and Miller, *Adv. Cancer Res.*, 1953, **1**, 387.
[13] Elbs, Hirschel, Wagner, Himmler, Türk, Henrich, and Lehmann, *J. prakt. Chem.*, 1924, **108**, 209.
[14] Chakrabarty and Dutt, *J. Indian Chem. Soc.*, 1928, **5**, 555.

(V; R = Me), m. p. 105—106°. The pure 2′-amino-4-dimethylaminoazobenzene (V; R = Me) exhibited an absorption maximum at 440—450 mμ (Fig. 2). The product of m. p. 133—134° is apparently a molecular complex which resists resolution by crystallisation. Reduction of the nitroazo-compound (II; R = CH_2·CH_2Cl) by ethanolic sodium sulphide, followed by chromatography, gave the thiazan (VI) as the only identifiable product; the formation of thiazans by the reaction of di-(2-chloroethyl)amines with sodium sulphide has been reported earlier.[15]

FIG. 2. *Absorption spectra in ethanol.*



A, 2′-Amino-4-dimethylaminoazobenzene (V; R = Me).
B, Elbs's compound, m. p. 133—134°.
C, 2-(p-Dimethylaminophenyl)benzotriazole (IV; R = Me).

It is of interest that the very slow hydrolysis of the 2-chloroethylamine (IV; R = CH_2·CH_2Cl), less than 1% under standard conditions,[16] confirms the base-weakening effect on arylamines of a *p*-(benzotriazol-2-yl) substituent observed by Elbs *et al.* (ref. 13, p. 223).

It was also desirable to discover whether a naturally occurring enzyme system could

TABLE 2. *Relative rates of reduction of a series of acidic derivatives of 4-di-(2-chloroethyl)-aminoazobenzene by xanthine oxidase–xanthine in pyrophosphate buffer* (pH 8·2) *in 30 min. at* 24°.

Subst.	Redn. (%)	Biol. acty.[a]	Subst.	Redn. (%)	Biol. acty.[a]	Subst.	Redn. (%)	Biol. acty.[a]
			(I; R = R′ = CH_2·CH_2Cl)					
2-CO_2H,4′-NO_2 ...	*ca.* 85[b]	+	2′-CO_2H	34	+	2′-SO_2H	2	—
2′-CO_2H,2-MeO ...	70	+	2-CO_2H,2′-CN	34	+	3′-CO_2H	2	—
2 : 4′-$(CO_2H)_2$	55	+	4′-SO_2H	5	—	(I; R = R′ = Me)		
2′-CO_2H,2-Me ...	49	+	4′-CO_2H,2-Me	4	+	2′-CO_2H (methyl-red)	72	
2′-CO_2H,2 : 4′-Me_2	42	+	4′-CO_2H	4	—			

[a] As inhibitors of the growth of the transplanted Walker rat carcinoma. [b] In 5 min.

effect reduction of the azo-linkage, for if this could be established and if the ease of reduction of a di-(2-chloroethyl)aminoazo-compound by such a system paralleled its biological activity then there would be a strong *a priori* case in favour of the hypothesis that activity

[15] Korshak and Strepikheev, *J. Gen. Chem.* (*U.S.S.R.*), 1944, **14**, 312; Cerkovnikov and Stern, *Arhiv Kem.*, 1946, **18**, 12; Ross, *J.*, 1950, 815.
[16] Ross, *J.*, 1949, 183.

depended on ease of reduction. Since various dyes are known to act as hydrogen acceptors in the xanthine oxidase–xanthine system it seemed logical to examine this enzyme. It was now necessary to work with entirely aqueous solutions, so the rates of reduction of various acidic derivatives, which have adequate water solubility at pH 8·2, were examined at 24° under anærobic conditions. The reaction did not proceed in accordance with any simple kinetic law, so the results are expressed in Table 2 as the percentage reduction in a given time. It had been established that the azo-compounds were unaffected by the enzyme alone or by xanthine alone under the standard conditions. Re-oxidation by iodine led to the re-formation of azo-compounds in the initial stages of the reaction (see above).

The correlation of biological activity with the ease of reduction of the azo-linkage has been discussed elsewhere [17] and it suffices here to indicate that the initial hypothesis has been supported by the results obtained for reduction in neutral solutions in the present work.

Experimental

Rates of Reduction of Azo-compounds in Acid Stannous Chloride.—Stannous chloride solution. A solution of stannous chloride dihydrate (50 g.) in ethanol (2 l.) was heated under reflux for 1 hr. and then distilled, 1½ l. being collected. 500 Ml. of this stabilised ethanol was introduced into the reservoir bottle of an automatic burette, and a stream of oxygen-free nitrogen was passed through the apparatus. When all the air had been displaced stannous chloride dihydrate (4·51 g.) was washed into the bottle with 2N-hydrochloric acid (500 ml.). Unless made up as described a turbid solution was obtained. The burette was subsequently operated by means of pure compressed nitrogen.

Solutions of azo-compounds. The concentration was 10^{-4}M, in redistilled absolute ethanol.

Determination of the relative velocity constant. 10 ml. of a solution of 4-di-(2-chloroethyl)-aminoazobenzene (A) and of a solution of the azo-compound under test (B) were placed in 50-ml. stoppered flasks. Stannous chloride solution (10 ml.) was rapidly run into flask (A), and the stopwatch was started. The thoroughly mixed solution was quickly transferred into a 1-cm. absorption cell and placed in the carrier (adapted for circulation of water at 24°) of a Unicam spectrophotometer. The optical density of the solution was measured after 2 min. against a control solution made by diluting the stannous chloride solution with an equal volume of absolute ethanol. At 3 min. stannous chloride solution was added to flask (B), and the contents were transferred to the Unicam carrier as before. Optical-density readings were taken at the following times: (A) 2, 4, 6, 8, 10, 12, 14 min.; (B) 5, 7, 9, 11, 13, 15, 17 min.

The following result for the 3′-methoxy-derivative of compound (I) is typical:

	Optical density (*D*)			Optical density (*D*)			Optical density (*D*)	
Time (min.)	(A) at 530 mμ *	(B) at 400 mμ *	Time (min.)	(A) at 530 mμ *	(B) at 400 mμ *	Time (min.)	(A) at 530 mμ *	(B) at 400 mμ *
2	0·715	—	8	0·386	—	13	—	0·118
4	0·582	—	9	—	0·269	14	0·209	—
5	—	0·602	10	0·313	—	15	—	0·078
6	0·475	—	11	—	0·181	16	0·173	—
7	—	0·408	12	0·257	—	17	—	0·047

* The wavelengths chosen were those of maximum absorption in 2N-acidic ethanol (see Part XVI I)

For very rapidly reduced compounds readings were required more frequently but the rate of reaction of the reference compound was always measured at the same time, usually by returning to solution (A) for measurements after reduction in solution (B) had reached 70—80% completion. By plotting time against the log *D* for the period 4—14 min. in the average run good straight lines were always obtained. This time interval was chosen when it was found that the contents of the cells attained a steady temperature after 3—4 min. From the ratio of of the slopes of the lines the relative unimolecular rate constant was obtained. In the above case 100 × slope B/slope A = 100 × 0·089/0·044 = 202. Values quoted in Table 1 are the result of at least two concordant runs. The pH of the solutions before and after reaction was 0·3, measured by using a glass-electrode.

Rates of Reduction of Azo-compounds in Hydrazine Solutions.—Hydrazine solution. Recrystallised hydrazine dihydrochloride (21 g.) was dissolved in N-sodium hydroxide (300 ml.) and water (200 ml.), and the filtered solution was stored under nitrogen in an automatic burette.

Solutions of azo-compounds were 10^{-4}M, prepared as above.

[17] Ross and Warwick, *Nature*, 1955, **176**, 298.

Determination of the relative velocity constant. The procedure was similar to that described above except that hydrazine solution (10 ml.) was run in to start the reaction. At the hydrazine concentration chosen the actual rate of reduction of the reference compound was practically the same in the two series of experiments. The relative rate constants were again evaluated graphically. The pH of the solution throughout the reaction was 8.

Rates of Reduction of Azo-compounds by Xanthine Oxidase–Xanthine.— Solutions of azo-compound. The acidic azo-compound (15 mg.) and xanthine (30 mg.) were dissolved in warm N-sodium hydroxide (2 ml.), and the cooled solution was diluted to 100 ml. with distilled water.

Buffer solution. Sodium pyrophosphate decahydrate (71·3 g.) and sodium hydrogen pyrophosphate (13·3 g.) were dissolved in water, and the solution made up to 2 l. This solution, to which chloroform (10 ml.) was added as preservative, had pH 8.

Reduction experiment. A solution of the azo-compound (3 ml.), pyrophosphate buffer (12 ml.), water (7 ml.) and N/50-hydrochloric acid (3 ml.) were mixed while oxygen-free nitrogen was passed through the mixture. After 10 min. xanthine oxidase solution (1 ml. of preparation stage M/5, see ref. 18) was added and the solution was rapidly transferred to a stoppered 1 cm. absorption cell. The cell, which was completely filled (no air-space), was used as above for measurement of the optical density at intervals (usually every 5 min.), against a control solution containing everything but the azo-compound. In a number of cases removal of the stopper from the cell to allow access of air increased the absorption in the region of the azo-*K*-band; the following run with methyl-red shows this effect.

Time (min.)	4	8	13	21	36	45	50	Stopper	59	68
D (400 mμ)	1·151	1·046	0·860	0·602	0·282	0·178	0·093	removed	0·120	0·134

Reduction of 4-Dialkylamino-2′-nitroazobenzenes with Ethanolic Ammonium Sulphide.— Hydrogen sulphide was passed into a solution of 4-dimethylamino-2′-nitroazobenzene (1 g.) and aqueous ammonia (10 ml.; *d* 0·880) in ethanol (150 ml.). When the solution had become pale yellow it was diluted with water and extracted with ether. The dried ether solution yielded the triazole oxide (III; R = Me) (0·85 g.), m. p. 165—167°, as pale yellow needles from ethanol, as described by Elbs *et al.*[18]

Similar reduction of 4-di-(2-chloroethyl)amino-2′-nitroazobenzene gave an almost quantitative yield of 2-[p-*di*-(2-*chloroethyl*)*aminophenyl*]*benzotriazole oxide monohydrate*, yellow plates, m. p. 133—134° (from ethanol) (Found: C, 51·7; H, 4·3; N, 15·1; Cl, 19·2. $C_{16}H_{16}ON_4Cl_2,H_2O$ requires C, 52·0; H, 4·3; N, 15·2; Cl, 19·3%).

Stannous Chloride Reduction of the Triazole Oxide (III; R = CH_2·CH_2Cl).—To a solution of the triazole oxide (2·0 g.) in ethanol (150 ml.) was added one of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.) and water (25 ml.). After 2½ hours' refluxing the ethanol was removed and an excess of aqueous sodium hydroxide was added. A dried benzene extract was passed through a column of activated alumina which retained unchanged oxide but allowed the *benzotriazole* (IV; R = CH_2·CH_2Cl) to pass through. The triazole formed pale yellow plates, m. p. 137—138°, from light petroleum (b. p. 60—80°) (Found: C, 57·0; H, 5·1; N, 16·9. $C_{16}H_{16}N_4Cl_2$ requires C, 57·3; H, 4·8; N, 16·7%).

Reduction of 4-Dialkylamino-2′-nitroazobenzenes with Ethanolic Sodium Sulphide.—A solution of the nitroamine (II; R = Me) (1·0 g.) in ethanol (30 ml.) was heated with a solution of sodium sulphide (3·5 g.) in water (3 ml.) for 1 hr. Addition of water to the cooled solution yielded an orange precipitate which was collected and repeatedly crystallised from ethanol. The product, which appeared to be homogeneous under the microscope, formed orange plates, m. p. 133—134°. When its benzene solution was passed through activated alumina two bands appeared. The fluorescent yellow band which was easily eluted contained the triazole (IV; R = Me), m. p. 183—184°, which was also obtained by reduction of the triazole oxide (III; R = Me) by stannous chloride. A more strongly adsorbed orange band was eluted with ether. It contained 2′-*amino*-4-*dimethylaminoazobenzene*, m. p. 105—106°, which formed orange plates from aqueous ethanol (Found: C, 70·1; H, 6·7; N, 23·1. $C_{14}H_{16}N_4$ requires C, 70·0; H, 6·7; N, 23·3%).

Similar reduction of 4-di-(2-chloroethyl)amino-2′-nitroazobenzene gave a sulphur-containing compound, m. p. 194°, colourless needles from benzene, as the only characterisable product. It is apparently 2-p-(*tetrahydro*-4-*thiazinyl*)*phenylbenzotriazole* (VI) (Found: C, 64·3; H, 5·3; N, 18·3; S, 10·4. $C_{16}H_{16}N_4S$ requires C, 64·8; H, 5·4; N, 18·9; S, 10·8%).

This investigation and that in the preceding paper were supported by grants made to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for

[18] Avis, Bergel, and Bray, *J.*, 1955, 1100.

Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, and was carried out during the tenure by one of us (G. P. W.) of an overseas C.S.I.R.O. research studentship. We thank Professor A. Haddow for permission to quote the results of tumour-growth inhibition studies and Professor F. Bergel, Mr. R. C. Bray, and Mr. P. Avis for making available to us a preparation of xanthine oxidase and for advice on its use.

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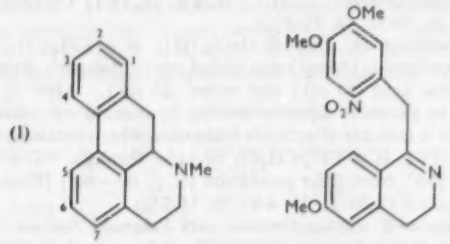
339. isoThebaine: The Synthesis of 2:3:6-Trimethoxyaporphine.

By K. W. BENTLEY and E. T. BLUES.

2:3:6-Trimethoxyaporphine has been synthesised by a combination of the Bischler–Napieralsky *iso*quinoline, and the Pschorr phenanthrene synthesis, and been found to differ from *iso*thebaine methyl ether.

THE alkaloid *iso*thebaine, which occurs in the roots of *Papaver orientale* after ripening and withering of the aerial parts,[1] was considered to be 4-hydroxy-3:5-dimethoxyaporphine [aporphine has the structure (I)] by Klee,[2] who degraded the methyl ether to 3:4:5-trimethoxyphenanthrene, a result subsequently confirmed by Schlittler and Müller.[3] This identity of the end-product of degradation with 3:4:5-trimethoxyphenanthrene has however been challenged by Kiselev and Konovalova[4] who for this reason rejected the structure suggested by Klee.

On biogenetic grounds Bentley and Cardwell[5] suggested that the alkaloid could be 2(or 4)-hydroxy-3:6(or 5)-dimethoxyaporphine. Of the possibilities embodied in this



suggestion one is the structure suggested by Klee; and the 4-hydroxy-3:6-dimethoxy- and the 2-hydroxy-3:6-dimethoxy-structure can be eliminated as *iso*thebaine methyl ether is not identical with morphothebaine dimethyl ether or with 2:3:6-trimethoxyaporphine, which was synthesised as described below. In view of these results, and of the fact that *iso*thebaine cannot be 5-hydroxy-3:6-dimethoxyaporphine since its methyl ether is not identical with *N*-methyltuduranine methyl ether, Kiselev and Konovalova's disagreement with the experimental work of Klee and of Schlittler and Müller can be discounted.

2:3:6-Trimethoxyaporphine was synthesised in the following way. 4:5-Dimethoxy-2-nitrophenylacetyl chloride was condensed with 2-*m*-methoxyphenylethylamine, and the resulting amide dehydrated with phosphorus pentachloride to 1-(4:5-dimethoxy-2-nitrobenzyl)-3:4-dihydro-6-methoxy*iso*quinoline (II), the methiodide of which with zinc and

[1] Gadamer, *Arch. Pharm.*, 1911, **249**, 39.
[2] Klee, *Arch. Pharm.*, 1914, **252**, 211.
[3] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 1119.
[4] Kiselev and Konovalova, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 148.
[5] Bentley and Cardwell, *J.*, 1955, 3252.

hydrochloric acid gave 1-(2-amino-4 : 5-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline. This base on diazotisation and treatment with zinc dust underwent Pschorr phenanthrene ring closure, yielding 2 : 3 : 6-trimethoxyaporphine. This base could not be induced to form a crystalline hydrogen (−)-tartrate as does *iso*thebaine methyl ether, and the ultraviolet spectrum of the synthetic base showed significant differences from that of *iso*thebaine; the two bases are clearly not identical.

Experimental

N-(4 : 5-Dimethoxy-2-nitrophenylacetyl)-2-m-methoxyphenylethylamine.—Phosphorus pentachloride (25 g.) was slowly added to a suspension of 4 : 5-dimethoxy-2-nitrophenylacetic acid (13·1 g.) in cold, dry chloroform (80 ml.), and when the reaction was complete the resulting solution of the acid chloride was added slowly, with vigorous stirring, to a mixture of 2-*m*-methoxyphenylethylamine (12 g.), chloroform (50 ml.) and 0·70N-aqueous sodium hydroxide (600 ml.), with ice-cooling. After 20 min. the chloroform layer was separated, the aqueous layer was extracted once with chloroform, and the combined chloroform solutions were washed with dilute acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). On evaporation of the chloroform a viscous oil was obtained and this was crystallised from methanol (yield 17·5 g.). The *amide* was obtained as yellow prisms, m. p. 156°, on recrystallisation from ethanol (Found : C, 60·7; H, 5·9; N, 7·3. $C_{19}H_{23}O_6N_2$ requires C, 60·9; H, 5·9; N, 7·5%).

1-(4 : 5-Dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-6-methoxyisoquinoline (II).—A solution of the foregoing amide (10 g.) and phosphorus pentachloride (12 g.) in chloroform (80 ml.) was set aside at 15° for 3 days. The solvent was removed *in vacuo*, the residue dissolved in boiling water, and the solution filtered. The sparingly soluble salt that separated when the solution was cooled was collected, dissolved in hot water, and decomposed with aqueous ammonia. The liberated base was collected and recrystallised from methanol, 1-(4 : 5-*dimethoxy-2-nitrobenzyl*)-3 : 4-*dihydro-6-methoxyisoquinoline* (7·5 g.) being obtained as colourless prisms, m. p. 172° (Found : C, 64·1; H, 5·7; N, 7·8. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%). The *methiodide*, prepared by refluxing the base with excess of methyl iodide for 30 min., was obtained from ethanol as yellow prisms, m. p. 182 (Found : C, 48·1; H, 4·5; N, 5·6; I, 25·3. $C_{19}H_{20}O_5N_2.CH_3I$ requires C, 48·1; H, 4·6; N, 5·6; I, 25·5%).

1-(2-Amino-4 : 5-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methylisoquinoline.—Zinc dust (25 g.) was slowly added to a stirred suspension of the nitrobenzyl*iso*quinoline methiodide (3·5 g.) in concentrated hydrochloric acid (80 ml.) and water (35 ml.) at 80—90°. The filtered solution was subsequently made alkaline with ammonia, and the liberated base extracted with ether. The ether extracts furnished a viscous oil, and the amino-compound was characterised as the *dihydrochloride*, colourless prisms, m. p. 240° (from ethanol) (Found : C, 57·6; H, 7·0; N, 6·8; Cl, 17·1. $C_{20}H_{26}O_3N_2.2HCl$ requires C, 57·7; H, 6·8; N, 6·8; Cl, 17·1%).

(±)-*2 : 3 : 6-Trimethoxyaporphine.*—1-(2-Amino-4 : 5-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline dihydrochloride (1·94 g.) in methanol (10 ml.) and 2N-sulphuric acid (10 ml.) was diazotised with aqueous sodium nitrite. The mixture was kept for 2 hr. at 10—15°, and then boiled under reflux for 1 hr., with the addition of concentrated hydrochloric acid (3 ml.) and zinc dust (5 g.). The filtered solution was made strongly alkaline with aqueous sodium hydroxide, and the precipitate extracted with ether. The ether extract yielded (±)-2 : 3 : 6-*trimethoxyaporphine* as an uncrystallisable oil. The *perchlorate* formed almost colourless prisms, m. p. 213°, from 50% ethanol (Found : C, 56·4; H, 5·2; N, 3·4; Cl, 8·2. $C_{20}H_{23}O_3N.HClO_4$ requires C, 56·6; H, 5·7; N, 3·3; Cl, 8·4%). The *methiodide* was obtained as almost colourless prisms, m. p. 207°, from aqueous ethanol (Found : C, 54·2; H, 5·2; N, 3·3; I, 27·5. $C_{20}H_{23}O_3N.CH_3I$ requires C, 54·0; H, 5·4; N, 3·0; I, 27·3%).

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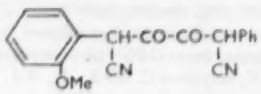
340. *Synthesis of Leprapinic Acid and Constitution of Pinastric Acid.*

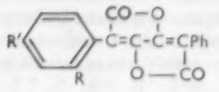
By O. P. Mittal and T. R. Seshadri.

Leprapinic acid has been synthesised by hydrolysis of α-*o*-methoxyphenyl-α′-phenylketipinic dinitrile to 2-methoxypulvinic dilactone followed by methanolysis. The nuclear methoxyl group of pinastric acid should be located in the phenyl ring near the ester grouping since the product of its condensation with *o*-phenylenediamine and subsequent hydrolysis contains a methoxyl group.

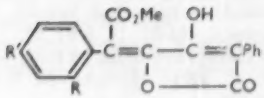
In an earlier communication,[1] leprapinic acid was shown to be 2-methoxyvulpinic acid (I). This has now been confirmed by its synthesis employing Asano's modification [2,3] (two stage) of Volhard's method.[4]



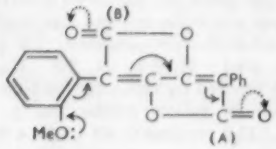
(II)



(III): R = OMe, R′ = H.
(V): R = H, R′ = OMe.

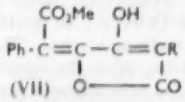


(I): R = OMe, R′ = H.
(VI): R = H, R′ = OMe.

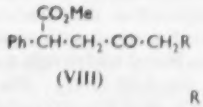


(IV)

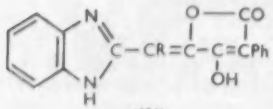
α-*o*-Methoxyphenyl-α′-phenylketipinic dinitrile[3] (II) was refluxed with sulphuric–acetic acid and then acetic anhydride. 2-Methoxypulvinic dilactone (III) was obtained, which when treated with methanolic potassium hydroxide yielded 2-methoxyvulpinic acid (I), identical with leprapinic acid.



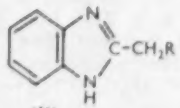
(VII)



(VIII)



(IX)



(X)

It follows that, of the two lactone rings in (III), the one closer to the substituted benzene nucleus is more easily opened. This seems to be according to expectations based on the availability of electrons in the bridging chain (cf. IV). Methoxyl being an electron source,

[1] Mittal and Seshadri, *J.*, 1955, 3053.
[2] Asano and Kameda, *Ber.*, 1934, **67**, 1522.
[3] *Idem*, *Ber.*, 1935, **68**, 1565.
[4] Volhard, *Annalen*, 1894, **282**, 1.

the positive charge on the carbon atom (A) will be considerably less than that on the carbon atom (B) which consequently receives the attack of the methoxide ion preferentially.

Since a similar method has been used [2] in the synthesis of pinastric acid from 4-methoxypulvinic dilactone (V), and since a *p*-methoxyl group will produce a similar electromeric effect, it is reasonable to expect that, in this synthesis also, the lactone ring near the substituted benzene ring should have undergone fission and hence this acid should also contain the methoxyl group in the phenyl ring near the ester group, as in (VI). This is, however, not in conformity with the findings of Asano and Kameda [3] who concluded that pinastric acid was 4'-methoxyvulpinic acid (VII) from a study of its reduction products, one of which was assigned the structure (VIII). To throw more light on this question the method suggested by Schönberg [5] and used earlier by Mittal and Seshadri [1] in the case of leprapinic acid has now been used with pinastric acid. This acid has been condensed with *o*-phenylenediamine and then subjected to fission with absolute alcoholic potassium hydroxide. The final product is 2-4'-methoxybenzylbenziminazole (X), identical with a synthetic sample obtained from *p*-methoxyphenylacetic acid, thus showing that the methoxyl group in pinastric acid also is attached to the benzene ring which is close to the ester group, *i.e.*, it is 4-methoxyvulpinic acid (VI).

Experimental

2-Methoxypulvinic Dilactone.—α-*o*-Methoxyphenyl-α'-phenylketipinic dinitrile was prepared according to the method of Asano and Kameda.[3] The intermediate ethyl cyano-*o*-methoxyphenylpyruvate melted at 95—96° (lit.[3], 104—105°) (Found: C, 62·5; H, 5·3. Calc. for $C_{13}H_{13}O_4N$: C, 63·1; H, 5·3%).

The dinitrile (0·5 g.), acetic acid (6 c.c.), concentrated sulphuric acid (3·3 c.c.), and water (4 c.c.) were heated under reflux for 2 hr. A reddish-brown oil gradually separated. When cooled and treated with water the oil solidified. The solid was filtered off, dried, and refluxed with acetic anhydride (5 c.c.) for ½ hr. The excess of the anhydride was decomposed with ice-water, and the yellow precipitate filtered off and dried (yield 0·5 g.). It crystallised from benzene as yellow needles, m. p. 172—173° (Found: C, 71·5; H, 3·7. Calc. for $C_{15}H_{12}O_5$: C, 71·2; H, 3·8%). The mixed m. p. with 2-methoxypulvinic dilactone obtained from leprapinic acid was undepressed.

Methyl 2-Methoxypulvinate (*Leprapinic Acid*).—2-Methoxypulvinic dilactone (0·25 g.) was dissolved in absolute methanolic potassium hydroxide (50 c.c.; 2%), kept at room temperature for ½ hr., diluted with water (150 c.c.), and acidified. The precipitate crystallised from methanol as golden-yellow rectangular tablets, m. p. 159—160° alone or mixed with leprapinic acid obtained from *Lepraria citrina* Schaer (Found: C, 67·6; H, 4·9. Calc. for $C_{20}H_{14}O_6$: C, 68·2; H, 4·6%).

Condensation of Pinastric Acid with o-Phenylenediamine.—Pinastric acid (0·7 g.), *o*-phenylenediamine (0·5 g.), and *NN*-dimethylaniline (25 c.c.) were refluxed at 200—210° for 4 hr. and, after cooling, poured into dilute acid (200 c.c.). The dark brown *2-(α-2-benziminazolyl-4-methoxybenzylidene)-3-hydroxy-5-oxo-4-phenylfuran* (IX) was filtered off, washed with dilute acid, then with water, and dried. It crystallised from ethyl acetate–light petroleum as brown-red rhombohedral plates, m. p. 292—293° (decomp.) (yield 0·3 g.) (Found: C, 73·4; H, 4·2. $C_{25}H_{18}O_4N_2$ requires C, 73·2; H, 4·4%). It dissolves with difficulty in benzene and ethyl alcohol and easily in ethyl acetate and in dilute alkali.

Hydrolysis. This product (150 mg.) was refluxed with absolute alcoholic potassium hydroxide (7 c.c.; 10%) for 5 hr. The insoluble potassium salts were filtered off and the filtrate was concentrated under reduced pressure. Ice-water (30 c.c.) was added, the semi-solid mass extracted with ether, and the ether extract dried and evaporated. The residual *2-4'-methoxybenzylbenziminazole* crystallised from ethyl acetate as colourless rectangular plates, m. p. 165—166° (Found: OCH_3, 12·4. $C_{15}H_{14}ON_2$ requires OCH_3, 13·1%) alone or mixed with a sample prepared from *p*-methoxyphenylacetic acid and *o*-phenylenediamine.

University of Delhi, Delhi. [*Received, December 6th*, 1955.]

[5] Schönberg and Sina, *J.*, 1946, 601.

341. *The Components of Wool Wax. Part III.* 7-Oxocholesterol and the Alleged Presence of Cholestanol.*

By A. H. Milburn and E. V. Truter.

Schoenheimer's alleged cholestanol,[1] isolated by fission of the digitonin complex obtained after the wool-wax alcohols have been brominated, contains mainly 7-oxocholesterol with some cholesterol dibromide and smaller and more variable amounts of lanostenol. Cholesta-3 : 5-dien-7-one is present only in samples obtained by decomposition of the digitonin complex under unsuitable conditions : it arises by dehydration of 7-oxocholesterol.

In 1930 Schoenheimer [1] described a method for determining what he considered to be the saturated congeners of cholesterol. The method is founded on the observation that cholesterol dibromide does not form an insoluble complex with digitonin, the percentages of sterol that could be precipitated with digitonin before and after treatment with bromine being determined. Treatment of the saturated sterols with sodium in boiling xylene causes coprostanol to epimerise and so to lose its ability to react with digitonin whereas cholestanol is, to a large extent, unaffected.[2] Schoenheimer used this observation to distinguish between the two natural isomers of dihydrocholesterol.[3]

Cholesterol concentrates from different sources were examined, and for wool wax it was found that 14—19% of the total digitonin-precipitable material (4—7% of the alcoholic fraction) was apparently saturated.[4] Although the identity of the saturated wool-wax sterols was not investigated further, the epimerisation test indicated that cholestanol was the main component of some samples from other sources. Later workers [5,6] have accepted the implication that cholestanol occurs in wool wax. However, chromatographic separations of the wool-wax alcohols in this laboratory led to the conclusion that the presence of cholestanol, in more than traces, was unlikely. Schoenheimer's experiments have, therefore, been repeated and extended, and completely different results have been obtained.

Wool-wax alcohols were brominated at 0° in ethanol and, after the insoluble dibromides had been filtered off, those compounds which still reacted with digitonin were precipitated. Subsequently, the digitonides were split by Bergmann's [7] or Dam and Schoenheimer's method.[8] In agreement with Schoenheimer's observations, the yield of "saturated" sterol obtained from the wool-wax alcohols varied from 4·8 to 6·4%.

Initially a number of samples of the "saturated" sterols (hereinafter called the S-fraction) were examined by different methods. Later the entire S-fraction was chromatographed on alumina in order to determine the approximate amounts of each component.

Elementary analysis of the S-fraction showed the presence of bromine. A change in the optical rotation from [α] +14° to +24° during three days indicated the presence of dibromocholesterol which is first precipitated as the 5α : 6β-isomer, [α] −44°, but slowly isomerises to the more stable 5β : 6α-isomer,[9] [α] +47°. Proof of the presence of cholesterol dibromide was obtained by debromination and identification of cholesterol. Contrary to Schoenheimer's generalisation from other observations it was found that more thorough washing of the digitonide from the brominated wool-wax alcohols did not yield an S-fraction containing appreciably less bromine. Cholesterol dibromide alone does not form an insoluble digitonide so that, in these circumstances, it must be occluded in, or co-precipitated with, the other insoluble digitonides.

* Part II, *J.*, 1954, 3344.

[1] Schoenheimer, *Z. physiol. Chem.*, 1930, **192**, 77.
[2] Windaus and Uibrig, *Ber.*, 1914, **47**, 2384; 1916, **49**, 1724.
[3] Schoenheimer, *Z. physiol. Chem.*, 1930, **192**, 86.
[4] Behring, Hummel, and Schoenheimer, *ibid.*, p. 93.
[5] Daniel, Lederer, and Velluz, *Bull. Soc. Chim. biol.*, 1945, **27**, 218.
[6] Truter, *Quart. Reviews*, 1951, **5**, 390.
[7] Bergmann, *J. Biol. Chem.*, 1940, **132**, 471.
[8] Dam and Schoenheimer, *Z. physiol. Chem.*, 1933, **215**, 59.
[9] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.

Treatment of the S-fraction with 2 : 4-dinitrophenylhydrazine followed by adsorption analysis disclosed 7-oxocholesterol and cholesta-3 : 5-dien-7-one. The presence of the latter in the S-fraction was surprising because it does not form a digitonin complex. Subsequently, two lines of evidence showed that it arose by dehydration of 7-oxocholesterol. First, if the digitonide was decomposed at room temperature cholestadienone could not be detected in the subsequent chromatographic fractionation. Secondly, the ultraviolet spectrum of the fresh digitonide showed a single absorption maximum at 238 mμ, but after the digitonide had been split with *hot* pyridine the resulting S-fraction showed absorption maxima at 238 and 280 mμ. The second maximum indicated that cholestadienone had been formed during the process.

Lanost-8-enol was identified after acetylation of the S-fraction and chromatography on alumina. It forms a moderately insoluble digitonide [10] so that its presence is not unexpected.

From preliminary elementary analyses the percentage of dibromide in fraction S was calculated, on the assumption that all the bromine was present as cholesterol dibromide; lanosterol dibromide may also be present but this has been ignored because lanosterol was not isolated from the products of debromination. Chromatography was then used to separate the known components of the mixture. The percentages, based upon the amounts of *purified* material, are as follows :

	Hartolan *	Laboratory wax
Lanost-8-enol (%)	20	—
7-Oxocholesterol (%)	38	70
Dibromide (calc. from the Br analysis; and includes 3% of cholesterol dibromide)	26	15
Total (%)	84	85
S-fraction (% of total alcohols)	4·8	6·3
Material not accounted for (% of total alcohols)	0·8	0·9

* Messrs. Croda, Ltd., Goole, Yorke.

No lanosterol was isolated from the laboratory wax although a fraction which amounted to 11% of the total gave the characteristic Liebermann–Burchardt colour reaction.

The Table shows that, as applied to wool-wax alcohols, Schoenheimer's technique gives an S-fraction which, as Schoenheimer himself claimed, comprises about 5% of the total. The composition of more than 80% of this material has now been elucidated but no evidence has been found to support the allegation that cholestanol is present—if it is, the quantity will not amount to 1%.

Experimental

Optical rotations were measured in $CHCl_3$, and ultraviolet spectra in EtOH.

Isolation of the "Saturated" Sterols.—A *ca.* N-solution of bromine in ethanol was slowly added to a vigorously stirred solution of wool-wax alcohols (20·05 g.) in absolute ethanol (450 ml.) cooled in ice, until a slight excess was present (starch–iodide). After 2 hr. the suspension was filtered and the residue was washed with ethanol (100 ml.). The crude cholesterol dibromide (4·91 g.) had $[\alpha]_D$ −38·5° (*c* 2·3) and m. p. 113°. By the addition of water to the filtrate the concentration of ethanol in it was adjusted to 96%. A 1% solution of digitonin in 96% ethanol (450 ml.) containing a slight excess of bromine was added, and the mixture was kept in the dark while the slight excess of bromine was maintained by occasional additions. After 48 hr. the precipitate was filtered off, washed with 96% ethanol (50 ml.) and with ether (2 × 50 ml.) (this is "the standard way") and dried at 80°. The product (4·77 g.) was very pale yellow.

In another experiment identical quantities of reagents were used, but the digitonide was washed by removing it from the sintered crucible and shaking it with ethanol (50 ml.), filtering the suspension, and repeating the treatment. This procedure was then repeated with ether (2 × 50 ml.). The bromine content of the digitonide washed in the standard manner was 1·71% while from the more carefully washed digitonide it was 1·73%.

[10] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759.

Recovery of Sterols from the Digitonide.—In the initial experiment the digitonide (4·64 g.) was dissolved in pure pyridine (75 ml.) on the water-bath (1 hr.). The solvent was then removed under reduced pressure and the residue was extracted (Soxhlet) with dry ether.[7] The residue (3·5 g.) was dissolved in boiling 85% ethanol (350 ml.) and after 24 hr. at room temperature the insoluble material was filtered off and treated with pyridine and ether as already described. Evaporation of the combined ethereal extracts yielded a yellow glass (1·23 g.), $[\alpha]_D$ −6°.

In subsequent experiments the digitonide (4·51 g.) was dissolved in dry pyridine (50 ml.) at room temperature, and the digitonin was precipitated by addition of ether (200 ml.). The precipitate (3·3 g.) was filtered off and dissolved in 85% ethanol (330 ml.) and the solution was set aside for 24 hr. The white deposit was filtered off and treated with pyridine and ether as indicated above. The combined ethereal extracts were washed with water, dilute hydrochloric acid, and then water, and dried (Na_2SO_4). Evaporation of the solvent afforded a pale yellow glass.

Separation of the Phenylhydrazones.—One crystallisation of the yellow glass (1·23 g.) from ethyl acetate–methanol (1 : 1; 5 ml.) gave a white powder (0·78 g.), m. p. 138°. Because the optical rotation of this material became progressively more dextrorotatory with time it was thought to contain cholesterol dibromide. The yellow glass obtained by evaporation of the mother-liquor was treated with a solution of 2 : 4-dinitrophenylhydrazine and cooled in ice. After 30 min. the precipitate (278 mg.) was filtered off and adsorbed on alumina (Brockmann No. 4; 1·5 × 50 cm.). 9 : 1 Light petroleum–benzene eluted the 2 : 4-dinitrophenylhydrazone (100 mg.) of cholesta-3 : 5-dien-7-one. Benzene eluted a further 44 mg. of unidentified material and finally benzene containing 1% of ethanol eluted the 2 : 4-dinitrophenylhydrazone of 7-oxocholesterol.

Cholesta-3 : 5-dien-7-one. Recrystallisation of the crude hydrazone from benzene–ethanol gave orange needles of cholesta-3 : 5-dien-7-one, m. p. and mixed m. p. 224—225° (Found : C, 70·8; H, 8·2; N, 9·7. Calc. for $C_{33}H_{46}O_4N_4$: C, 70·5; H, 8·2; N, 9·95%), $\lambda_{max.}$ 265 (log ε 4·3) and 397 mμ (log ε 4·5) [lit. : $\lambda_{max.}$ 265 (log ε 4·3) and 397 mμ (log ε 4·5)], $[\alpha]_D$ −380° (*c* 0·382). An attempt to split the 2 : 4-dinitrophenylhydrazone by Robinson's method [11] using 99% formic acid and copper carbonate yielded a tar.

7-Oxocholesterol. The 2 : 4-dinitrophenylhydrazone of 7-oxocholesterol was obtained as yellow needles (from chloroform–methanol), m. p. and mixed m. p. 246—247°, $[\alpha]_D$ −607° (*c* 0·28), $\lambda_{max.}$ 258 (log ε 4·24) and 385 mμ (log ε 4·47) (Found : C, 67·9; H, 8·35; N, 9·65. Calc. for $C_{33}H_{46}O_5N_4$: C, 68·2; H, 8·3; N, 9·65%).

Lanostenol. A portion of the S-fraction (0·692 g.) was crystallised from methanol (5 ml.) and then from ethyl acetate–methanol (3 ml.) to give white needles (80 mg.), m. p. 145°, $[\alpha]_D$ +60° (*c* 0·41), of lanost-8-enol (Found : C, 84·25; H, 12·0. Calc. for $C_{30}H_{52}O$: C, 84·0; H, 12·2%). The acetate (needles, from ethyl acetate–methanol after purification on alumina) had m. p. 120°, $[\alpha]_D$ +58° (*c* 0·38) (Found : C, 81·95; H, 11·2. Calc. for $C_{32}H_{54}O_2$: C, 81·7; H, 11·5%). The 3 : 5-dinitrobenzoate had m. p. 207° (lit., m. p. 208°), and the benzoate had m. p. 192—192·5°, $[\alpha]_D$ +69° (*c* 1·03) (lit., m. p. 194°, $[\alpha]_D$ +68°).

Composition of the S-Fraction derived from Hartolan.—The S-fraction (1·475 g.) was chromatographed on acid-washed and reactivated alumina (1 × 20 cm.). Six fractions were eluted : E1 (light petroleum), 343 mg.; E2 (1 : 4 benzene–light petroleum), 44 mg.; E3 (4 : 1 benzene in light petroleum), 106 mg.; E4 (benzene), 376 mg.; E5 (ether), 435 mg., and E6 (1% of methanol in ether), 114 mg.

Lanostenol. Fraction E1 was further purified by adsorption on alumina and recrystallisation from ethyl acetate–methanol, to give needles (294 mg.), m. p. and mixed m. p. 144°, $[\alpha]_D$ +61°. The benzoate (needles from methanol) had m. p. 193°, $[\alpha]_D$ +69° (*c* 1·83) (Found : C, 83·0; H, 10·6. Calc. for $C_{37}H_{56}O_2$: C, 83·3; H, 10·7%).

Cholesterol. Fractions E2, E3, and E4 contained bromine. They were combined, dissolved in ethanol, and debrominated by refluxing with sodium iodide for 3 hr. The cold solution was then diluted with ether, and the ethereal solution washed with aqueous sodium sulphite, then with water, and dried (Na_2SO_4). Distillation of the ether and crystallisation of the residue from methanol gave cholesterol (50 mg.), m. p. 147·5°, $[\alpha]_D$ −39° (*c* 1·31) (Found : C, 83·9; H, 11·9. Calc. for $C_{27}H_{46}O$: C, 84·0; H, 11·9%). It gave an acetate, m. p. and mixed m. p. 114° (Found : C, 81·1; H, 10·9. Calc. for $C_{29}H_{48}O_2$: C, 81·2; H, 11·2%), and a benzoate, m. p. (to an anisotropic liquid) 149°, $[\alpha]_D$ −14·4° (*c* 1·13) (Found : C, 82·9; H, 10·0. Calc. for

[11] Robinson, *Nature*, 1954, **173**, 541.

$C_{34}H_{50}O_2$: C, 83·2; H, 10·2%). The original S-fraction contained 8·02% of bromine which corresponds to a cholesterol dibromide content of 26%.

7-Oxocholesterol. Fractions E5 and E6 were combined and recrystallised to give 7-oxocholesterol (white needles from aqueous methanol), m. p. and mixed m. p. 170°, $[\alpha]_D$ −102° (*c* 0·505), λ_{max} 238 mμ (log ε 4·1) (Found: C, 80·5; H, 10·8. Calc. for $C_{27}H_{44}O_2$: C, 80·8; H, 11·0%). Its acetate had m. p. and mixed m. p. 155°, $[\alpha]_D$ −95° (*c* 0·42) (Found: C, 78·7; H, 10·3. Calc. for $C_{29}H_{46}O_3$: C, 78·6; H, 10·45%).

Composition of the S-Fraction derived from a Laboratory-extracted Wax.—Wax was extracted from Australian merino wool (64s) by means of peroxide-free ether, and was hydrolysed at room temperature by sodium methoxide. After the alcohols (13 g.) had been isolated they were processed as indicated above, and yielded a brominated fraction (2·9 g.) and an S-fraction (0·82 g.). The S-fraction was chromatographed on neutral alumina (1 × 20 cm.). Three main fractions were obtained: F1 (27 mg.) was eluted with 3 : 7 benzene–light petroleum; F2 (67 mg.) with benzene; and F3 (456 mg.) with ether.

Fraction F2 contained bromine. It did not crystallise even after purification on alumina. The bromine analysis of the original S-fraction (Br, 4·34%) suggests a dibromosterol content of 15%.

Fraction F3 was 7-oxocholesterol (white needles from methanol; 418 mg.), m. p. and mixed m. p. 170°, $[\alpha]_D$ −103° (*c* 0·5). The 2 : 4-dinitrophenylhydrazone had m. p. 247°, $[\alpha]_D$ −592° (*c* 0·3) (Found: C, 68·25; H, 8·2. Calc. for $C_{33}H_{48}O_5N_4$: C, 68·2; H, 8·3%).

Cholesta-3 : 5-dien-7-one was synthesised by Marker and Whittle's method.[12] Cholesterol (55 g.) was dissolved in thionyl chloride (55 ml.) and set aside for 24 hr. The product was stirred with acetone and filtered and the residue recrystallised from acetone, to give pale yellow needles of cholesteryl chloride (37·5 g.), m. p. 96·5°.

7-Oxocholesteryl chloride. During 1 hr. a solution of chromium trioxide (26 g.) in 50% aqueous acetic acid (36 ml.) was added to a vigorously stirred solution of cholesteryl chloride (30 g.) in acetic acid (600 ml.) at 55°. After 2 hr. the excess of chromium trioxide was destroyed by ethanol, the solution concentrated to one-third of its volume, and water (15 ml.) added. The crystalline chloro-ketone (8 g.) deposited from the cold solution had m. p. 144—145°.

Cholesta-3 : 5-dien-7-one. 7-Oxocholesteryl chloride (7·5 g.) was heated under reflux for 2 hr. with potassium hydroxide (7N; 240 ml.) in 94% ethanol. After removal of the ethanol, water was added and the ketone was extracted with ether. Evaporation of the ether gave a brown residue which was purified by adsorption on alumina. The first fraction to be eluted with light petroleum was the desired ketone (cream-coloured prisms from ethanol; 2·3 g.), m. p. 114° (Found: C, 84·7; H, 11·1. Calc. for $C_{27}H_{42}O$: C, 84·8; H, 11·0%). The 2 : 4-dinitrophenylhydrazone (orange needles from chloroform–methanol) had m. p. 225—226° (Found: C, 70·7; H, 8·1; N, 10·0. Calc. for $C_{33}H_{44}O_4N_4$: C, 70·5; H, 8·2; N, 9·95%).

7-Oxocholesterol. During 2 hr. chromium trioxide (9·1 g.) in 50% aqueous acetic acid (12 ml.) was added to a vigorously stirred solution of cholesteryl acetate (13 g.) in acetic acid (140 ml.) at 55°. After a further 2 hr. the excess of trioxide was destroyed by ethanol, and the solution was concentrated to one-third of its bulk. On cooling, the crude keto-ester was deposited; it was recrystallised twice from ether (m. p. 156; 2 g.). Hydrolysis of the acetate (1·4 g.) at room temperature with sodium methoxide afforded 7-oxocholesterol (white needles from aqueous methanol; 0·5 g.), m. p. 170°. The 2 : 4-dinitrophenylhydrazone (yellow needles from chloroform–methanol) had m. p. 246°, $[\alpha]_D$ −610° (*c* 0·2) (Found: C, 67·9; H, 8·4; N, 9·8. Calc. for $C_{33}H_{48}O_5N_4$: C, 68·2; H, 8·3; N, 9·65%).

The authors are indebted to Professor J. B. Speakman for his interest and encouragement, and to the International Wool Secretariat for financial assistance.

Textile Chemistry Laboratory, University, Leeds, 2. [*Received, December 12th*, 1955.]

[12] Marker and Whittle, *J. Amer. Chem. Soc.*, 1937, **59**, 619.

342. *The Components of Wool Wax. Part IV.* The Identification of Some Steroidal Derivatives.*

By A. H. Milburn, E. V. Truter, and F. P. Woodford.

Cholestane-3β : 5α : 6β-triol, 7-oxocholesterol, and 3β-hydroxylanost-8-en-7-one and 3β-hydroxylanost-8-en-7 : 11-dione have been isolated from commercial wool-wax alcohols by chromatography on alumina.

The alcoholic fraction of wool wax contains about 20% of long-chain aliphatic alcohols which can be easily extracted by treatment with urea.[1,2] The residue, which consists, as far as is known, of steroids and trimethyl-steroids, was resolved on a large-scale, somewhat unorthodox, chromatographic "column." Alumina, instead of being packed in a vertical column, was placed in stoppered bottles, and the solvent was progressively decanted through the series. Seventy-nine fractions were eventually obtained by development of the chromatogram with benzene, the course of the separation being followed by means of the optical rotation. Although each fraction still contained a mixture, it was found that different components were concentrated in particular fractions. Detailed examination of some of these fractions has, so far, led to the identification of four new wool-wax components, namely, cholestane-3β : 5α : 6β-triol, 7-oxocholesterol, 3β-hydroxylanost-8-en-7-one and 3β-hydroxylanost-8-en-7 : 11-dione.

The diketone has been described by Ruzicka *et al.*[3] It has been characterised through its acetate[3,4] and the acetate of the corresponding saturated ketol.[5,6] 3β-Hydroxylanosten-7-one has been prepared by Mijovic *et al.*[7] and by Knight *et al.*[8] by different routes. Neither of these compounds has been isolated from natural sources hitherto. Because very mild oxidation of lanostenyl acetate gives the 7-oxo-derivative which can in turn be oxidised to 7 : 11-dioxolanostenyl acetate, both compounds may be the products of autoxidation.

The presence of 7-oxocholesterol was suspected by Daniel *et al.*[9] They found that the quantity of cholesta-3 : 5-dien-7-one that could be isolated varied with the conditions of hydrolysis of the wax. Hot alkaline saponification gave high yields whereas hydrolysis in the cold gave very low yields of the dienone. They postulated that a 7-oxocholesteryl ester was the precursor, but 7-oxocholesterol itself was not isolated. After the conclusion of the work described here, Panizo and Bilbao[10] reported the isolation of 7-oxocholesterol from Spanish merino wool wax. Contrary to our experience, and also that of Daniel *et al.*[9] and of Mauthner and Suida,[11] these authors state that the higher the temperature at which the wax is saponified the greater is the yield of 7-oxocholesterol.

The preceding paper describes the isolation of 7-oxocholesterol by means of its digitonin complex. In the present study it was easily obtained by chromatography on alumina.

The cholestane-triol was isolated from the most strongly adsorbed fractions. Its physical constants and those of its derivatives agreed well with those of a synthetic sample, but the elementary analysis, despite careful drying, persistently showed a low carbon content. As no difficulty was encountered in the analysis of the synthetic compound, it seemed that the impurity in the natural triol might be a congener which is not removed by recrystallisation. After purification *via* its diacetate, the natural triol gave a satisfactory analysis. The possibility that the natural product was contaminated with traces of

* Part III, preceding paper.

[1] von Rudloff, *Chem. and Ind.*, 1951, 338.
[2] Tiedt and Truter, *ibid.*, p. 911.
[3] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472.
[4] Cavalla and McGhie, *J.*, 1951, 834.
[5] Dorée, McGhie, and Kurzer, *J.*, 1948, 988.
[6] Voser, Montavon, Gunthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893.
[7] Mijovic, Voser, Heusser, and Jeger, *ibid.*, 1952, **35**, 964.
[8] Knight, McGhie, and Birchenough, *Chem. and Ind.*, 1953, 822.
[9] Daniel, Lederer, and Velluz, *Bull. Soc. Chim. biol.*, 1945, **27**, 218.
[10] Panizo and Bilbao, *Publ. Inst. Quím. Alonso Barba*, 1954, **8**, 181.
[11] Mauthner and Suida, *Monatsh.*, 1896, **105**, 565.

aluminium compounds which had been eluted from the chromatographic column, was also examined; no aluminium could be detected. Apart from this observation the wool-wax compound appeared to be identical with the synthetic one. The mixed melting point of the diacetates was undepressed, and the infrared spectra of the natural triol and its diacetate were identical with those of the synthetic specimens. The triol was characterised by oxidation to the 5-hydroxy-diketone which was dehydrated to the 4 : 5-unsaturated diketone.

Experimental

Optical rotations were measured in $CHCl_3$, and ultraviolet spectra in EtOH.

Removal of the Long-chain Alcohols.[8]—Commercial wool-wax alcohols (300 g.; "Hartolan," Messrs. Croda, Ltd.) were dissolved in benzene–chloroform (1500 : 750 ml.) and the solution was poured on finely powdered urea (450 g.) which had been moistened with methanol (90 ml.). After 19 days, during which the mixture was occasionally stirred, the solids were filtered off and washed with benzene (250 ml.). The filtrate and washings were combined and treated with more urea (100 g.) moistened with methanol (20 ml.). Nine days later the solids were filtered off, washed with benzene (100 ml.), and united with the solids from the previous treatment with urea. The filtrate was washed with water (3 × 500 ml.), and the solvent was distilled off. The residue, consisting of polycyclic alcohols, was a red glass. The urea complex was decomposed with water and the long-chain alcohols were filtered off (yield 64 g.; m. p. 59—63°).

Separation by Adsorption.—Activated alumina was placed in 79 stoppered bottles of 450 ml. capacity. The first 25 bottles each contained 100 g. of alumina of low activity (Brockmann V); the next 25 each contained 50 g. of alumina (Brockmann V), and each of the remaining bottles held 50 g. of alumina (Brockmann I). The polycyclic alcohols (300 g.) were dissolved in benzene (500 ml.) to give a clear solution. Subsequent dilution with benzene precipitated the more polar alcohols which did not re-dissolve, even after dilution to 8 l. The precipitate (21 g.) was filtered off and an aliquot part of the solution (400 ml.) was poured into bottle 1. After the alumina had been thoroughly stirred and allowed to settle, the supernatant liquid was poured into bottle 2, and a further aliquot part of solution (400 ml.) into bottle 1. In this manner the entire volume was distributed in 16 bottles; later, benzene was used to develop the system until it occupied 79 bottles. The optical rotation of the supernatant liquids was used as a guide to the course of the separation. Each bottle yielded two fractions for more detailed examination: the mixture of alcohols dissolved in the supernatant liquid (recovered by evaporation to dryness), and the mixture of alcohols adsorbed on the alumina (recovered by extraction with chloroform in a Soxhlet apparatus). In some cases these fractions were combined.

7 : 11-*Dioxolanost-8-en-3-ol.* The canary-yellow solid from bottle 47 (5 g.) was dissolved in light petroleum–benzene (9 : 1) and adsorbed on alumina (Brockmann IV; 1·5 × 85 cm. column). Elution with increasingly polar solvents gave nine fractions: A, 256 mg., $[\alpha]_D$ +9°, was eluted with light petroleum–benzene (9 : 1); B, 33 mg., $[\alpha]_D$ −85°, light petroleum–benzene (4 : 1); C, 755 mg., $[\alpha]_D$ +14°; D, 417 mg., $[\alpha]_D$ +29°; E, 1481 mg., $[\alpha]_D$ +33°; F, 1125 mg., $[\alpha]_D$ 0° (all light petroleum–benzene; 1 : 1); G, 312 mg., $[\alpha]_D$ +57, benzene; H, 799 mg., $[\alpha]_D$ +54°, benzene–ether (4 : 1); I, 208 mg., $[\alpha]_D$ 0°, ether. Fractions G and H were combined and adsorbed on a second column of alumina (Brockmann IV; 1 × 10 cm.). The first fraction was eluted with benzene, the next five with benzene–ether (9 : 1), and the last two with benzene–ether (1 : 1). The amounts were: GH1, 31 mg., [α] 0°; GH2, 48 mg., [α] −30°; GH3, 238 mg., [α] +103°; GH4, 373 mg., [α] +42°; GH5, 175 mg., [α] +63°; GH6, 59 mg., [α] +25°; GH7, 85 mg., [α] +33°; GH8, 132 mg., [α] +25°.

Fraction GH3 was 3β-hydroxylanost-8-ene-7 : 11-dione (pale yellow needles from methanol). It appeared to melt at 112—114°, solidify as the temperature was raised, and melt again at 142·5—143·5° (Ruzicka *et al.*[3] give m. p. 113—115°), $[\alpha]_D$ +98° (*c* 0·71), $\lambda_{max.}$ 272 mμ (log ε 3·9) (Found: C, 78·4; H, 10·6. Calc. for $C_{30}H_{48}O_3$: C, 78·8; H, 10·6%). Acetylation with acetic anhydride at 50° gave a monoacetate, m. p. 157·5—158°, $[\alpha]_D$ +90° (*c* 0·318), $\lambda_{max.}$ 272 mμ (log ε 3·94) {lit., m. p. 157°, [α] +90°, $\lambda_{max.}$ 273 mμ (log ε 3·95)}. The acetate (50 mg.) was dissolved in boiling glacial acetic acid (10 ml.), and zinc dust (0·6 g.) was slowly added. After the mixture had been heated under reflux for 1 hr. it was cooled and diluted with water, and the ester was extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4), and after evaporation to dryness the residue was recrystallised from methanol, to give plates of 7 : 11-dioxolanostanyl acetate, m. p. 223° (lit., 223°), $[\alpha]_D$ +65° (*c* 0·198) (Found: C, 76·9; H, 10·5. Calc. for $C_{32}H_{54}O_4$: C, 76·75; H, 10·5%).

3β-Hydroxylanost-8-en-7-one. The alcohols from bottle 43 (2·74 g.) were combined with fractions GH 4—8 and adsorbed on alumina (Brockmann IV; 2 × 90 cm.), and the eluates were combined into fractions: B1, 755 mg., [α] −40°, eluted with light petroleum–benzene (2 : 1); B2, 177 mg. [α] +83°, and B3, 241 mg., [α] +31°, with light petroleum–benzene (1 : 1); B4, 461 mg., [α] +30°, with light petroleum–benzene (1 : 3).

Fraction B1 consisted mainly of cholesterol, and fraction B2 of 3β-hydroxylanost-8-en-7 : 11-dione. Fraction B3 yielded 3β-hydroxylanost-8-en-7-one (white needles from methanol), m. p. 136, $[\alpha]_D$ +30° (*c* 0·406), $\lambda_{max.}$ 255 mμ (log ε 3·94) (Found: C, 81·0; H, 11·1. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). The acetate (needles from acetonitrile) had m. p. 151°, $[\alpha]_D$ +22° (*c* 0·45), $\lambda_{max.}$ 255 mμ (log ε 3·99) {values recorded in the literature are: m. p. 151°;[4] 151° and 157°;[9] 155°,[12] $[\alpha]_D$ +20°, $\lambda_{max.}$ 255 mμ (log ε 4·1)} (Found: C, 79·4; H, 10·7. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%).

Fraction B4 was obtained as needles (from ether–hexane), m. p. 223°, $\lambda_{max.}$ 259 mμ (log ε 2·5). It formed a monoacetate (in acetic anhydride at 50° for 30 min.), m. p. 185° (Found: C, 76·6; H, 10·5. Calc. for $C_{33}H_{54}O_4$: C, 76·75; H, 10·5%). The diacetate (obtained by acetic anhydride–pyridine) had m. p. 132°. This substance appears to be a mixture of 3β : 11α-dihydroxylanost-8-en-7-one, m. p. 228°, $\lambda_{max.}$ 252 mμ (log ε 3·95), which gives a monoacetate, m. p. 185°, and a diacetate, m. p. 132°, and 3β : 11α-dihydroxylanostan-7-one, m. p. 216° (diacetate, m. p. 134°).

Cholestane-3β : 5α : 6β-triol. (*a*) From wool wax: The alcohols extracted from the alumina of bottles 5—10 were re-adsorbed on alumina (Brockmann V) and, after extensive washing of the column with chloroform, 1 : 9 methanol–ether eluted the triol (needles from methanol), m. p. 238° (decomp.), $[\alpha]_D$ 0° (in MeOH) (Found, after drying *in vacuo* at 30° for 48 hr.: C, 76·3; H, 11·15; after purification *via* the acetate: C, 77·0; H, 11·4. Calc. for $C_{27}H_{48}O_3$: C, 77·1; H, 11·5%). The diacetate (needles from aqueous methanol) had m. p. and mixed m. p. 167°, $[\alpha]_D$ −40° (*c* 0·63) (Found: C, 73·6; H, 10·8. Calc. for $C_{31}H_{52}O_5$: C, 73·75; H, 10·4%).

(*b*) Synthetic cholestanetriol, prepared by the method of Pickard and Yates,[13] had m. p. 238° (decomp.), $[\alpha]_D$ 0° (in MeOH) (Found, after drying *in vacuo* at room temperature: C, 77·2; H, 11·6%). The diacetate had m. p. 165—166°, $[\alpha]_D$ −39° (Found: C, 73·5; H, 10·6%).

5α-Hydroxycholestane-3 : 6-dione. (*a*) Wool-wax cholestanetriol (405 mg.) in 90% acetic acid (20 ml.) and benzene (4 ml.) was oxidised with sodium dichromate dihydrate (191 mg.) at 0° for 22 hr. After dilution with water the product was extracted with ether. Removal of the solvent afforded the dione (needles from ethanol; 355 mg.), m. p. 231° (decomp.), $[\alpha]_D$ −21° (*c* 4·8). In agreement with Fieser's observation [14] it was found that very slow cooling of the solution gave needles having a higher m. p., *e.g.*, 242° and 248° (Found: C, 77·4; H, 10·4. Calc. for $C_{27}H_{44}O_3$: C, 77·8; H, 10·6%). There was no ultraviolet absorption band.

(*b*) Synthetic triol (2 g.) was oxidised with chromium trioxide (1·4 g.) in glacial acetic acid (185 ml.) at 5° for 16 hr. Purification of the product, as above, gave the dione, m. p. 231° (decomp.), $[\alpha]_D$ −19° (*c* 9·6) (Found: C, 77·3; H, 10·8%).

Cholest-4-ene-3 : 6-dione. (*a*) Synthetic dione (516 mg.) was dissolved in dry chloroform (60 ml.), and dry hydrogen chloride was bubbled through the solution at 0° for 30 min. The yellow product afforded pale yellow plates (296 mg.) (from aqueous ethanol), m. p. 130°, $[\alpha]_D$ −14°, $\lambda_{max.}$ 252 and 307 mμ. Fractional crystallisation from ethanol gave cholest-4-ene-3 : 6-dione as yellow plates, m. p. 120°, $\lambda_{max.}$ 251 mμ (log ε 4·02). The less soluble fraction was obtained as yellow needles, m. p. 164—165°, $[\alpha]_D$ +1°, $\lambda_{max.}$ 308 and 251 mμ (log ε 4·18 and 3·89).

(*b*) Hydroxycholestadione from wool wax was dehydrated as described under (*a*). The product was a yellow glass, $[\alpha]_D$ −23°, $\lambda_{max.}$ 252 (principal) and 308 mμ (weak).

7-Oxocholesterol. The contents of bottles 32 and 33 were chromatographed separately. Fractions rich in 7-oxocholesterol were combined (567 mg.; $[\alpha]_D$ −38°) and re-adsorbed on another alumina column (Brockmann V; 1·4 × 55 cm.). Four fractions were eluted with benzene: U1, 9 mg.; U2, 105 mg., [α] −87°; U3, 131 mg. [α] −94°; and U4, 20 mg. [α] −79°. Fractions U2 and U3 afforded 7-oxocholesterol (needles from light petroleum), m. p. 169—170°, $[\alpha]_D$ −103° (*c* 1·021), $\lambda_{max.}$ 238 mμ (log ε 4·13) (Found: C, 80·8; H, 11·0. Calc. for $C_{27}H_{44}O_2$: C, 80·95; H, 11·1%). It gave an acetate, m. p. and mixed m. p. 155—156°, $[\alpha]_D$ −95° (*c* 1·0), $\lambda_{max.}$ 237 mμ (log ε 4·09) (Found: C, 78·3; H, 10·3. Calc. for $C_{29}H_{46}O_3$: C, 78·6; H, 10·45%). The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 246—247°,

[12] Barton, Fawcett, and Thomas, *J.*, 1951, 3147.
[13] Pickard and Yates, *J.*, 1908, 1678.
[14] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4386.

$[\alpha]_D$ −600°, $\lambda_{max.}$ 258 and 385 mμ (log ε 4·24 and 4·46) (Found : C, 67·9; H, 8·4; N, 9·8. Calc. for $C_{32}H_{48}O_5N_4$: C, 68·2; H, 8·3; N, 9·65%).

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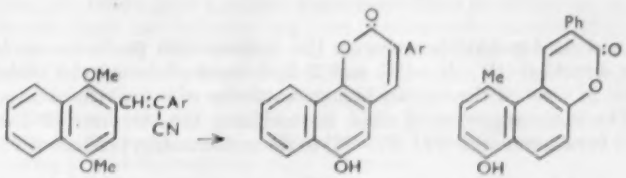
TEXTILE CHEMISTRY LABORATORY, UNIVERSITY, LEEDS, 2. [*Received, December 12th*, 1955.]

343. *Further Studies of Dihydroxynaphthalenes.*

By NG. PH. BUU-HOÏ and DENISE LAVIT.

Syntheses are reported of several mono- and di-substituted derivatives of dihydroxy- and dimethoxy-naphthalenes (methyl homologues, allyl and benzyl derivatives, aldehydes, ketones), and the positions of the substituents are discussed. The conversion of dihydroxynaphthalenes into benzocoumarins and other heterocyclic sytems is investigated.

IT was recently found that treatment of dimethoxynaphthalenes with dimethylformamide, and Wolff–Kishner reduction of the resulting dimethoxynaphthaldehydes, provided a convenient route to methyl-substituted dihydroxynaphthalenes.[1] This method has now been applied to the preparation of methyl-substituted 1 : 4- and 1 : 6-dihydroxynaphthalene. Formylation of 1 : 4-dimethoxynaphthalene readily gave 1 : 4-dimethoxy-2-naphthaldehyde, which Sah [2] claimed to have obtained by a Gattermann reaction from 1 : 4-dimethoxynaphthalene but whose properties differed considerably from those reported by that author. The constitution of our aldehyde was established, not only by the preparation therefrom of 1 : 4-dihydroxy-2-methylnaphthalene, but also by formation, with arylacetonitriles, of acrylonitriles (I), which gave 3-aryl-6-hydroxy-7 : 8-benzocoumarins (II) on demethylation with pyridine hydrochloride; this reaction proves the *ortho*-position of the aldehyde function in respect of a methoxy-group.



(I) (II) (III)

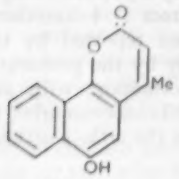
In the 1 : 6-dihydroxynaphthalene group, 1 : 6-dihydroxy-4-methylnaphthalene was prepared by demethylation of 4 : 7-dimethoxy-1-methylnaphthalene; formylation of this ether gave 2 : 5-dimethoxy-8-methyl-1-naphthaldehyde, in whose molecule the *ortho*-position of the formyl group was confirmed by conversion of its condensation product with benzyl cyanide into the benzocoumarin (III). Reduction of this aldehyde, followed by demethylation, led to 1 : 6-dihydroxy-4 : 5-dimethylnaphthalene, which was rapidly oxidised in air; an even greater autoxidability was encountered in the isomeric 4-ethyl-1 : 6-dihydroxynaphthalene, whose dimethyl ether was prepared by reduction of 1-acetyl-4 : 7-dimethoxynaphthalene.

In the 1 : 5-dihydroxynaphthalene series, the zinc chloride-catalysed reaction of benzyl chloride with its dimethyl ether yielded a mixture of 4-benzyl- and 4 : 8-dibenzyl-1 : 5-dimethoxynaphthalene; demethylation with pyridine hydrochloride, however, afforded the free dihydroxy-compound only from the disubstituted product, the monobenzyl derivative being converted into a compound containing more oxygen than that in

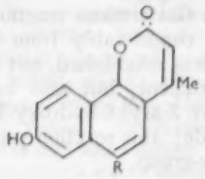
[1] Buu-Hoï and Lavit, *J.*, 1955, 2776.
[2] Sah, *Rec. Trav. chim.*, 1940, **59**, 1029, 1032, 1035.

the expected 4-benzyl-1 : 5-dihydroxynaphthalene. In the 2 : 7-dihydroxynaphthalene series, the constitution of 2 : 7-dimethoxy-1-naphthaldehyde was rigidly proved by oxidation to 2 : 7-dimethoxy-1-naphthoic acid; had the formyl group, by analogy with bromination of 2 : 7-dimethoxynaphthalene,[4] entered position 3, 3 : 6-dimethoxy-2-naphthoic acid would have resulted. The last named acid, first synthesised by Sunthankar and Gilman [5] by carboxylation of the lithio-derivative of 2 : 7-dimethoxynaphthalene, was now obtained by oxidation, with sodium hypobromite, of 2-acetyl-3 : 6-dimethoxynaphthalene, prepared by Friedel–Crafts acetylation of 2 : 7-dimethoxynaphthalene, proving thereby that formylation and Friedel–Crafts acylation follow different courses in this series. An attempt to prepare 2 : 7-dihydroxy-1 : 8-di-*n*-propylnaphthalene by dehydrogenation of the product of a Claisen rearrangement of 2 : 7-diallyloxynaphthalene was unsuccessful, because this rearrangement-product was highly autoxidisable and could not be obtained pure.

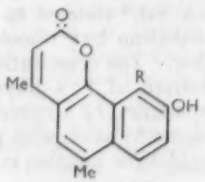
2 : 7-Dimethoxy-1-naphthaldehyde and 2 : 7-dimethoxy-8-methyl-1-naphthaldehyde readily condensed with arylacetonitriles to give acrylonitriles, which were converted into 3-aryl-2′-hydroxy-5 : 6-benzocoumarins; similarly, coumarins were obtained by demethylation of the acrylonitriles derived from 2 : 6-dimethoxy- and 2 : 6-dimethoxy-5-methyl-1-naphthaldehyde. Although condensation of α- and β-naphthol with β-ketonic esters has frequently been used for the preparation of coumarins,[6] the behaviour of dihydroxynaphthalenes in this reaction has hitherto been investigated only in the case of 1 : 5-dihydroxynaphthalene.[7] It was now found that 1 : 4-dihydroxynaphthalene readily gave 6-hydroxy-4-methyl-7 : 8-benzocoumarin (IV) with ethyl acetoacetate; for 1 : 6-dihydroxy-



(IV)

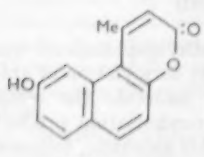


(V)

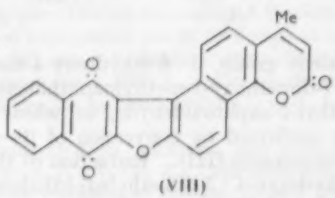


(VI)

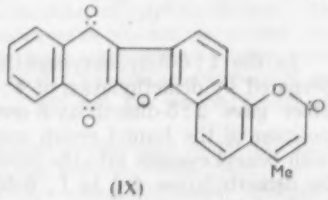
naphthalene and its 4-methyl homologue, the condensation products can be formulated as 2′-hydroxy-4-methyl- (V; R = H) and 2′-hydroxy-4 : 6-dimethyl-7 : 8-benzocoumarin (V; R = Me), in view of the known higher reactivity of α-naphthol compared with the β-isomer.[8] The same argument is valid for assigning the structure of 3′-hydroxy-4 : 6-dimethyl-7 : 8-benzocoumarin (VI; R = H) to the condensation product of 1 : 7-dihydroxy-



(VII)



(VIII)



(IX)

4-methylnaphthalene. From the same viewpoint, an interesting difference was noted between 2 : 6- and 2 : 7-dihydroxynaphthalene, the former giving no condensation product with ethyl acetoacetate, whilst the latter gave 2′-hydroxy-4-methyl-5 : 6-benzocoumarin

[3] Buu-Hoï and Khenissi, *J.*, 1951, 2307.
[4] Ioffe and Fedorova, *J. Gen. Chem.* (*U.S.S.R.*), 1936, **6**, 1079; Bell, personal communication.
[5] Sunthankar and Gilman, *J. Org. Chem.*, 1951, **16**, 8.
[6] Von Pechmann and Cohen, *Ber.*, 1884, **17**, 2187; Bartsch, *Ber.*, 1903, **36**, 1966; Bargellini, *Gazzetta*, 1925, **55**, 945; Baker, *J.*, 1925, **127**, 2349.
[7] Robinson and Weygand, *J.*, 1941, 386; Shamshurin, *J. Gen. Chem.* (*U.S.S.R.*), 1944, **14**, 885.
[8] Appel, *J.*, 1935, 1031.

(VII). 1-Hydroxy-5-methoxynaphthalene readily gave 1′-methoxy-4-methyl-7 : 8-benzocoumarin, which underwent demethylation with pyridine hydrochloride to the 1′-hydroxy-compound previously described by Robinson and Weygand.[7]

Condensation of 2 : 3-dichloro-1 : 4-naphthaquinone with 2′- and 1′-hydroxy-4-methyl-7 : 8-benzocoumarin in the presence of pyridine afforded 4′-methylcoumarino(7′ : 8′-4 : 3)-(VIII) and 4′-methylcoumarino(7′ : 8′-1 : 2)-brasan-5 : 10-quinone (IX) respectively; these high-melting compounds belong to a new type of complex oxygen-heterocyclic system.

Experimental

1 : 4-*Dimethoxy-2-naphthaldehyde*.—1 : 4-Dimethoxynaphthalene (91 g.; b. p. 175°/18 mm.) was prepared by methylation of 1 : 4-dihydroxynaphthalene (100 g.) with dimethyl sulphate (181 g.) and 10% aqueous potassium hydroxide (77 g.). A mixture of this dimethyl ether (50 g.), dimethylformamide (25 g.), dry toluene (50 c.c.), and phosphorus oxychloride (47 g.) was refluxed for 10 hr. with frequent shaking; on cooling, concentrated aqueous sodium acetate was added, and the mixture refluxed for 30 min. The aldehyde was then taken up in benzene, the benzene solution washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. 1 : 4-*Dimethoxy-2-naphthaldehyde* (25 g.), b. p. 199—200°/16 mm., formed stable, pale yellow needles, m. p. 117° (from ethanol), giving a red halochromy in sulphuric acid (Found : C, 72·2; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). The product obtained by Sah[8] from a Gattermann reaction with 1 : 4-dimethoxynaphthalene, and considered to be 1 : 4-dimethoxy-2-naphthaldehyde, melted between 60° and 65° and darkened rapidly in the air; it was probably a mixture containing demethylation products of the aldehyde sought. 1 : 4-*Dimethoxy-2-naphthaldehyde thiosemicarbazone* formed yellowish prisms, m. p. 252° (decomp. >225°), from acetic acid (Found : C, 57·8; H, 5·0. $C_{14}H_{15}O_2N_3S$ requires C, 58·1; H, 5·2%).

1 : 4-*Dihydroxy-2-methylnaphthalene*.—A mixture of the foregoing aldehyde (28 g.), 95% hydrazine hydrate (12 g.), and diethylene glycol (150 c.c.) was heated until dissolution occurred; potassium hydroxide (12 g.) was then added, and heating renewed for a further 30 min. at 190—200°, with removal of water. After cooling, water was added, and the reduction product was taken up in benzene, washed first with dilute hydrochloric acid, then with water, dried (Na_2SO_4), and fractionated *in vacuo*; 1 : 4-dimethoxy-2-methylnaphthalene (21 g.) b. p. 170—171°/14 mm., n_D^{24} 1·6086, gave a picrate which crystallised as red prisms, m. p. 91°, from ethanol. A mixture of this dimethyl ether (2 g.) and pyridine hydrochloride (12 g.) was refluxed for 10 min., water was added after cooling, and the demethylation product was taken up in ether; the ethereal solution was washed with a little cold water and dried (Na_2SO_4), and the residue from evaporation of the solvent recrystallised from toluene. 1 : 4-Dihydroxy-2-methylnaphthalene formed colourless needles, m. p. 175°, becoming grey in the air. The m. p. recorded[9] varies from 160° to 177—178°. The procedure described here provides a convenient method for preparing this biologically important substance.

6-*Hydroxy-4-methyl-7 : 8-benzocoumarin* (IV).—A cooled solution of 1 : 4-dihydroxynaphthalene (4 g.) and ethyl acetoacetate (10 g.) in ethanol (40 c.c.) was saturated with hydrogen chloride, and the mixture kept for 4 hr.; the precipitated *product* was collected, dried, and recrystallised from toluene, giving yellow prisms (3·2 g.), m. p. 206° (Found : C, 74·0; H, 4·6. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·4%).

β-(1 : 4-*Dimethoxy-2-naphthyl*)-α-*phenylacrylonitrile* (I; Ar = Ph).—A solution of 1 : 4-dimethoxy-2-naphthaldehyde (5 g.) and benzyl cyanide (2·7 g.) in warm ethanol (100 c.c.) was shaken with a few drops of 20% aqueous sodium hydroxide, and the mixture kept for 30 min.; the oil obtained on dilution with water solidified to a crystalline mass (6 g.). Recrystallisation from ethanol afforded pale yellow needles, m. p. 120°, giving a red halochromy in sulphuric acid (Found : C, 81·9; H, 5·5. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4%). Similar *acrylonitriles* are listed in Table 1.

6-*Hydroxy-3-phenyl-7 : 8-benzocoumarin* (II; Ar = Ph).—The foregoing nitrile (5·5 g.) was treated with boiling pyridine hydrochloride (35 g.) for 10 min., water added on cooling, and the mixture refluxed for 5 min.; the precipitate formed yellow needles (3·6 g.), m. p. 272° (from ethanol–toluene), whose solutions gave a strong green fluorescence (Found : C, 79·0; H, 4·1. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·2%). Similar *coumarins* are listed in Table 2.

[8] Fries and Lohmann, *Ber.*, 1921, **54**, 2912; Sah, *loc. cit.*; MacCorquodale *et al.*, *J. Biol. Chem.*, 1939, **131**, 357; Giral, *Anales. Fis. Quim.*, 1933, **31**, 861.

TABLE 1. *αβ-Disubstituted acrylonitriles.*[a]

	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
α-*p*-Chlorophenyl-β-(1 : 4-dimethoxy-2-naphthyl)-	140°	$C_{21}H_{16}O_2NCl$	71·9	4·8	72·0	4·6
α-*o*-Chlorophenyl-β-(1 : 4-dimethoxy-2-naphthyl)-	123	$C_{21}H_{16}O_2NCl$	71·8	4·9	72·0	4·6
α-*p*-Bromophenyl-β-(1 : 4-dimethoxy-2-naphthyl)-	144	$C_{21}H_{16}O_2NBr$	63·8	4·0	63·9	4·1
β-(1 : 4-Dimethoxy-3-methyl-2-naphthyl)-α-phenyl-[b] ...	149	$C_{22}H_{19}O_2N$	79·9	5·8	80·2	5·8
β-(2 : 7-Dimethoxy-1-naphthyl)-α-phenyl-	116	$C_{21}H_{17}O_2N$	79·8	5·5	80·0	5·4
α-*p*-Chlorophenyl-β-(2 : 7-dimethoxy-1-naphthyl)-	141	$C_{21}H_{16}O_2NCl$	72·2	4·5	72·0	4·6
α-*p*-Bromophenyl-β-(2 : 7-dimethoxy-1-naphthyl)-	161	$C_{21}H_{16}O_2NBr$	63·6	4·0	63·9	4·1
β-(2 : 7-Dimethoxy-8-methyl-1-naphthyl)-α-phenyl- ...	117	$C_{22}H_{19}O_2N$	80·4	5·7	80·2	5·8
β-(2 : 6-Dimethoxy-1-naphthyl)-α-phenyl-	128	$C_{27}H_{17}O_2N$	79·9	5·4	80·0	5·4
α-*p*-Chlorophenyl-β-(2 : 6-dimethoxy-1-naphthyl)-	157	$C_{21}H_{16}O_2NCl$	71·9	4·8	72·0	4·6
β-(2 : 6-Dimethoxy-5-methyl-1-naphthyl)-α-phenyl- ...	132	$C_{22}H_{19}O_2N$	80·0	6·0	80·2	5·8
α-*p*-Chlorophenyl-β-(2 : 8-dimethoxy-5-methyl-1-naphthyl)-	190	$C_{22}H_{18}O_2NCl$	72·2	4·8	72·5	5·0
β-(2 : 5-Dimethoxy-8-methyl-1-naphthyl)-α-phenyl- ...	139	$C_{22}H_{19}O_2N$	80·0	5·8	80·2	5·8
β-(1-Methoxy-4-methyl-2-naphthyl)-α-phenyl-	86	$C_{21}H_{17}ON$	84·2	5·8	84·3	5·7

[a] All substances were crystallised from ethanol; the halochromy in sulphuric acid varied from red to brown, except for the last substance which gave a green colour.

[b] This nitrile was prepared from benzyl cyanide and the formylation product of 1 : 4-dimethoxy-2-methylnaphthalene; this aldehyde was characterised as its *thiosemicarbazone*, pale yellow needles, m. p. 223° (decomp. >205°) (from ethanol) (Found: C, 59·1; H, 5·5. $C_{15}H_{17}O_2N_3S$ requires C, 59·4; H, 5·6%).

TABLE 2. *3-Substituted benzocoumarins.*[a]

Benzocoumarins	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-*p*-Chlorophenyl-6-hydroxy-7 : 8-[b]	306°	$C_{15}H_{11}O_3Cl$	70·7	3·2	70·6	3·4
3-*o*-Chlorophenyl-6-hydroxy-7 : 8-	299	$C_{15}H_{11}O_3Cl$	70·2	3·3	70·6	3·4
3-*p*-Bromophenyl-6-hydroxy-7 : 8-	324	$C_{15}H_{11}O_3Br$	62·4	3·1	62·1	3·0
6-Hydroxy-5-methyl-3-phenyl-7 : 8-	240	$C_{20}H_{16}O_3$	79·1	4·5	79·4	4·6
6-Methyl-3-phenyl-7 : 8-	164	$C_{20}H_{16}O_2$	83·6	5·1	83·9	4·9
2′-Hydroxy-3-phenyl-5 : 6-	258	$C_{19}H_{12}O_3$	78·9	4·4	79·2	4·2
3-*p*-Chlorophenyl-2′-hydroxy-5 : 6-	288	$C_{19}H_{11}O_3Cl$	70·3	3·3	70·6	3·4
3-*p*-Bromophenyl-2′-hydroxy-5 : 6-	307	$C_{19}H_{11}O_3Br$	61·9	3·2	62·1	3·0
2′-Hydroxy-1′-methyl-3-phenyl-5 : 6-	261	$C_{20}H_{16}O_3$	79·3	4·5	79·4	4·6
3′-Hydroxy-3-phenyl-5 : 6-	261	$C_{19}H_{12}O_3$	79·3	4·1	79·2	4·2
3-*p*-Chlorophenyl-3′-hydroxy-5 : 6-	277	$C_{19}H_{11}O_3Cl$	70·3	3·2	70·6	3·4
3′-Hydroxy-4′-methyl-3-phenyl-5 : 6-	299	$C_{20}H_{16}O_3$	79·3	4·5	79·4	4·6
3-*p*-Chlorophenyl-1′-hydroxy-4′-methyl-5 : 6-	335	$C_{20}H_{13}O_3Cl$	71·0	4·0	71·2	3·9
4′-Hydroxy-1′-methyl-3-phenyl-5 : 6-	254	$C_{20}H_{16}O_3$	79·1	4·6	79·4	4·6

[a] All substances were crystallised from ethanol–toluene or acetic acid, forming pale yellow or grey-tinged needles, soluble in aqueous alkalis to yellow solutions; the toluene solutions showed strong fluorescence.

[b] The structures of this and the four following substances resemble that of naphthotocopherol, a cyclisation product of α-phylloquinol possessing both vitamin E and vitamin K activities (Tishler, Fieser, and Wendler, *J. Amer. Chem. Soc.*, 1940, **62**, 1982).

1 : 6-*Dihydroxy-4-methylnaphthalene.*—A mixture of 1 : 6-dimethoxy-4-methylnaphthalene[10] (3 g.) and pyridine hydrochloride (18 g.) was refluxed for 8 min., and water (40 c.c.) was added after cooling; the demethylation-product was taken up in ether, the ethereal solution washed with water and dried (Na_2SO_4), and the residue quickly crystallised twice from benzene (charcoal). The *dihydroxy-compound* (1·8 g.) formed grey-tinged, autoxidisable needles, m. p. 132°, giving yellow alkaline solutions (Found: C, 75·6; H, 5·7. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%). After a brief boiling of its pyridine (5 c.c.) solution with 2 : 3-dichloro-1 : 4-naphthaquinone, this compound (0·25 g.) yielded a *brasanquinone*,[11] as sublimable, brown-red needles (0·3 g.; from nitrobenzene), m. p. >350°, giving a turquoise-blue halochromy in sulphuric acid (Found: C, 76·8; H, 3·9. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

2 : 5-*Dimethoxy-8-methyl-1-naphthaldehyde.*—A mixture of 1 : 6-dimethoxy-4-methylnaphthalene (16·5 g.), dimethylformamide (8 g.), phosphorus oxychloride (14·5 g.), and toluene (5 c.c.) was refluxed for 6 hr., and the mixture worked up in the usual way. Distillation *in vacuo* gave a mixture (16 g.) boiling at 227—229°/17 mm., which yielded on fractional recrystallisation

[10] Buu-Hoï and Lavit, *Bull. Soc. chim. France*, 1955, 1419.
[11] Buu-Hoï, *J.*, 1952, 489.

from ethanol: (*a*) 2 : 5-*dimethoxy*-8-*methyl*-1-*naphthaldehyde* (8 g.), pale yellow prisms, m. p. 98° (Found: C, 73·3; H, 5·9. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%) [*thiosemicarbazone*, yellowish needles, m. p. 276° (decomp. >250°), from acetic acid (Found: C, 59·1; H, 5·4. $C_{15}H_{17}O_2N_3S$ requires C, 59·4; H, 5·6%)], and (*b*) an isomeric *aldehyde* (0·6 g.), possibly 1 : 6-dimethoxy-4-methyl-2-naphthaldehyde, pale yellow needles, m. p. 90°, showing a depression of m. p. on admixture with the main product (Found: C, 72·8; H, 6·0%).

1 : 6-*Dihydroxy*-4 : 5-*dimethylnaphthalene*.—2 : 5-Dimethoxy-8-methyl-1-naphthaldehyde (5 g.) yielded on the usual Wolff–Kishner reduction 1 : 6-*dimethoxy*-4 : 5-*dimethylnaphthalene* (4 g.), pale yellow oil, b. p. 187—188°/17 mm., $n_D^{26\cdot5}$ 1·5995, which solidified to prisms, m. p. 48° (Found: C, 77·7; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%), giving a picrate, deep orange needles, m. p. 96° (from ethanol). 1 : 6-*Dihydroxy*-4 : 5-*dimethylnaphthalene*, obtained on demethylation, formed readily autoxidisable, grey-tinged needles, m. p. 153—154°, from benzene (Found: C, 76·3; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

1-*Acetyl*-4 : 7-*dimethoxynaphthalene*.—To a cooled solution of 1 : 6-dimethoxynaphthalene (26·5 g.) and acetyl chloride (13 g.) in dry nitrobenzene (125 c.c.), aluminium chloride (21 g.) was added in portions with stirring, and the mixture kept overnight at room temperature. After decomposition with water and steam-distillation of the solvent, the product was worked up in the usual way, and gave a *ketone*, b. p. 232—235°/20 mm., crystallising as colourless needles (20 g.), m. p. 67°, from ethanol (Found: C, 72·9; H, 6·3. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

2-(4 : 7-*Dimethoxy*-1-*naphthyl*)*cinchoninic Acid*.—A solution of the foregoing ketone (3 g.), isatin (2·1 g.), and potassium hydroxide (2·2 g.) in ethanol (50 c.c.) was refluxed for 24 hr.; water was then added, the neutral impurities were removed by ether-extraction and the aqueous layer was acidified with acetic acid. The *cinchoninic acid* (95% yield) formed yellowish needles, m. p. 226°, from ethanol (Found: C, 73·4; H, 4·9. $C_{22}H_{17}O_4N$ requires C, 73·5; H, 4·7%). Thermal decarboxylation afforded 2-(4 : 7-*dimethoxy*-1-*naphthyl*)*quinoline*, colourless prisms, m. p. 121° (from ethanol) (Found: C, 79·7; H, 5·7. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4%).

4-*Ethyl*-1 : 6-*dimethoxynaphthalene*.—Wolff–Kishner reduction of 1-acetyl-4 : 7-dimethoxynaphthalene (13 g.) gave a very poor yield of 4-*ethyl*-1 : 6-*dimethoxynaphthalene* (2·5 g.) as a pale yellow oil, b. p. 196—197°/20 mm., n_D^{26} 1·6040 (Found: C, 77·7; H, 7·4. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%); demethylation afforded an alkali-soluble, viscous yellow oil, which rapidly became a black resin on exposure to the air.

2′-*Hydroxy*-4-*methyl*-7 : 8-*benzocoumarin* (V; R = H).—Obtained in 80% yield from 1 : 6-dihydroxynaphthalene (4 g.) and ethyl acetoacetate (10 g.) in ethanol (40 c.c.) saturated with hydrogen chloride, this *coumarin* formed colourless, sublimable needles, m. p. 260° (nitrobenzene), soluble in aqueous alkali with a greenish-yellow colour (Found: C, 74·0; H, 4·6. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·4%).

4′-*Methylcoumarino*(7′ : 8′-4 : 3)*brasan*-5 : 10-*quinone* (VIII).—A solution of the foregoing coumarin (0·3 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (0·3 g.) in dry pyridine (5 c.c.) was refluxed for 30 min.; the precipitated *product* was washed with benzene, and recrystallised as brown needles, m. p. >350° (nitrobenzene), giving a deep violet halochromy in sulphuric acid (Found: C, 75·6; H, 2·9. $C_{24}H_{12}O_5$ requires C, 75·8; H, 3·2%).

2′-*Hydroxy*-4 : 6-*dimethyl*-7 : 8-*benzocoumarin* (V; R = Me).—Prepared from 1 : 6-dihydroxy-4-methylnaphthalene (1 g.) and ethyl acetoacetate (2·5 g.) in ethanol (10 c.c.), this *coumarin* (1·2 g.) formed yellowish, sublimable needles, m. p. 323°, from nitrobenzene (Found: C, 74·7; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

3′-*Hydroxy*-4 : 6-*dimethyl*-7 : 8-*benzocoumarin* (VI; R = H).—This *coumarin* (0·6 g.), prepared from 1 : 7-dihydroxy-4-methylnaphthalene (0·75 g.) and ethyl acetoacetate (2 g.), formed yellowish leaflets, m. p. 321°, from nitrobenzene (Found: C, 74·8; H, 4·8%); 3′-*hydroxy*-4 : 6 : 4′-*trimethyl*-7 : 8-*benzocoumarin* (VI; R = Me), obtained from 1 : 7-dihydroxy-4 : 8-dimethylnaphthalene (0·75 g.), formed pale yellow, sublimable needles (0·5 g.), m. p. 315°, from nitrobenzene (Found: C, 75·3; H, 5·2. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

Benzylation of 1 : 5-*Dimethoxynaphthalene*.—A solution of this dimethyl ether (50 g.) and benzyl chloride (34 g.) in dry chloroform (500 c.c.) was refluxed with finely powdered zinc chloride (15 g.) for 6 hr., water was added, and the chloroform layer was washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). Fractionation *in vacuo* of the residue from evaporation of the solvent yielded: (*a*) 4-*benzyl*-1 : 5-*dimethoxynaphthalene* (22 g.), b. p. 253—255°/14 mm., which crystallised as colourless needles, m. p. 115°, from ethanol (Found: C, 81·8; H, 6·3. $C_{19}H_{18}O_2$ requires C, 82·1; H, 6·5%); demethylation with pyridine hydrochloride gave a solid which crystallised from acetic acid as yellowish needles, m. p. 161°, which contained more oxygen than the expected 4-benzyl-1 : 5-dihydroxynaphthalene; (*b*)

4 : 8-*dibenzyl*-1 : 5-*dimethoxynaphthalene*, b. p. 310—312°/20 mm., crystallising as colourless leaflets (3 g.), m. p. 234°, from benzene (Found : C, 84·9; H, 6·3. $C_{26}H_{24}O_2$ requires C, 84·8; H, 6·5%); demethylation afforded 4 : 8-*dibenzyl*-1 : 5-*dihydroxynaphthalene*, an autoxidisable compound which formed colourless needles, m. p. 198°, from aqueous acetic acid (Found : C, 84·2; H, 5·7. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%).

1′-*Methoxy*-4-*methyl*-7 : 8-*benzocoumarin*.—A water-cooled solution of 1-hydroxy-5-methoxynaphthalene (4 g.) and ethyl acetoacetate (10 g.) in ethanol (40 c.c.) was saturated with hydrogen chloride for 2 hr., then left overnight. The precipitate obtained was washed with ethanol, and gave on recrystallisation grey-tinged prisms, m. p. 190° (from toluene) (Found : C, 75·1; H, 5·2. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). Demethylation with pyridine hydrochloride yielded 1′-hydroxy-4-methyl-7 : 8-benzocoumarin,[7] m. p. 302—303°.

4′-*Methylcoumarino*(7′ : 8′-1 : 2)*brasan*-5 : 10-*quinone* (IX), prepared by boiling for 5 min. a solution of 1′-hydroxy-4-methyl-7 : 8-benzocoumarin and 2 : 3-dichloro-1 : 4-naphthaquinone, formed brown-red prisms, m. p. > 350° (from nitrobenzene), giving a brown-violet halochromy with sulphuric acid (Found : C, 75·5; H, 3·0%).

2-*Acetyl*-3 : 6-*dimethoxynaphthalene*.—To an ice-cooled solution of 2 : 7-dimethoxynaphthalene (23 g.) and acetyl chloride (10 g.) in nitrobenzene (200 c.c.), aluminium chloride (18 g.) was added in portions with stirring, and the mixture left overnight at room temperature, then worked up in the usual way. The *ketone* (6·5 g.), b. p. 210—211°/12 mm., formed colourless needles, m. p. 65°, from light petroleum (Found : C, 72·8; H, 6·3%). It condensed with veratraldehyde in ethanol containing a few drops of aqueous sodium hydroxide, to give 3 : 6-*dimethoxy*-2-(3 : 4-*dimethoxycinnamoyl*)*naphthalene*, pale yellow needles, m. p. 109° (from ethanol) (blood-red halochromy in sulphuric acid) (Found : C, 72·9; H, 5·7. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·8%).

2-(3 : 6-*Dimethoxy*-2-*naphthyl*)*cinchoninic Acid*.—This *acid*, obtained by heating for 48 hr. a solution of 2-acetyl-3 : 6-dimethoxynaphthalene (2 g.), isatin (1·4 g.), and potassium hydroxide (1·5 g.) in ethanol (30 c.c.), formed pale yellow needles (0·5 g.), m. p. 230°, from ethanol (Found : C, 73·2; H, 4·8%).

3 : 6-*Dimethoxy*-2-*naphthoic Acid*.—To an aqueous solution of sodium hypobromite (prepared from 1·2 c.c. of bromine and 2·8 g. of sodium hydroxide in 13 c.c. of iced water), a solution of 2-acetyl-3 : 6-dimethoxynaphthalene (2 g.) in dioxan (5 c.c.) was added, and the mixture shaken for 1 hr.; the aqueous layer was then decanted, treated with a few c.c. of aqueous sodium hydrogen sulphite, and acidified with hydrochloric acid. 3 : 6-Dimethoxy-2-naphthoic acid [8] formed colourless needles (1 g.), m. p. 185°, from benzene. 2 : 7-Dimethoxy-1-naphthoic acid, prepared in poor yield by oxidation of the corresponding aldehyde (5 g.) with silver oxide (4 g.) in water at 60°, formed colourless prisms, m. p. 122°, from ligroin. Adams *et al.*[13] gave m. p. 112—113°.

Derivatives of 2 : 7-*Dihydroxynaphthalene*.—(*a*) A solution of 2 : 7-dihydroxynaphthalene (20 g.) and allyl bromide (34 g.) in acetone (200 c.c.) was refluxed with potassium carbonate (38 g.) for 3 hr., and the mixture poured into water. The supernatant oil was decanted, the allyl bromide in excess was evaporated, and the solid mass obtained recrystallised from ethanol, giving 2 : 7-*diallyloxynaphthalene* (8 g.) as colourless needles, m. p. 62° (Found : C, 79·9; H, 6·7. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); the picrate formed orange needles, m. p. 77°. Claisen rearrangement of this product, by boiling its diethylaniline solution for 1 hr., yielded an oil which darkened rapidly in the air and from which no solid derivative could be prepared.

(*b*) 2′-*Hydroxy*-4-*methyl*-5 : 6-*benzocoumarin* (VII), prepared by keeping for 48 hr. a solution of 2 : 7-dihydroxynaphthalene (4 g.) and ethyl acetoacetate (10 g.) in ethanol (40 c.c.) saturated with hydrogen chloride, formed grey-tinged needles (1·2 g.), m. p. 277°, from nitrobenzene (Found : C, 74·0; H, 4·2%). No coumarin was obtained under the same conditions with 2 : 6-dihydroxynaphthalene.

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[13] Adams, Miller, McGrew, and Anderson, *J. Amer. Chem. Soc.*, 1942, **64**, 1795.

344. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part I. The Addition of Bromotrichloromethane and Butanal to Unsaturated Acids, Esters, and Nitriles.*

By R. L. Huang.

The homolytic addition of bromotrichloromethane and butanal to unsymmetrical olefins CHR:CHR′ (ethyl crotonate, crotonic acid, ethyl hydrogen maleate, ethyl β-acetylacrylate, ethyl cinnamate, and *cis*- and *trans*-cinnamonitrile) has been studied. Since, steric factors being absent, addition proceeds *via* the radical (say CHXR·CHR′·) of the greater stability, identification of the adduct in each case affords a comparison of the stabilising effect of R and R′ on the alkyl radical. It is thus shown that the relative effects are: Ph > CO_2Et, CN; CO > CO_2Et > CO_2H > Me.

The properties of free alkyl radicals differ markedly according to the nature of substituent groups, exhibiting extreme activity in free methyl and ethyl, and relative stability in free benzyl and other radicals containing unsaturated groups. In general, substituent groups capable of resonance with the free radical centre confer stability, as in the free radicals derived from alkylbenzenes,[1] allylbenzene,[2] ketones,[3] etc. No attempt, however, has yet been made to compare the relative stabilising effects of such groups; this work concerns such a study.

It is now established that, where steric factors do not intervene, the course of a homolytic reaction depends on the relative stability of the intermediate free radical involved (for a review, see Huang [4]). In the addition, therefore, of a substance XY to an unsymmetrical olefin CHR:CHR′ by the usual chain mechanism involving, say, the addition of X· as the initiating step (reaction 1), the intermediate alkyl radical (I) or (II) would be formed according to whether R or R′, respectively, confers the greater stability on the intermediate radical. [Haszeldine's postulate [5] need not be considered here since both (I) and (II) contain the same number of hydrogen atoms at the radical centre.] Two products are therefore possible and, provided steric factors are absent or unimportant, identification of the adduct would reveal whether R or R′ is more effective as a stabilising substituent:

$$X\cdot + CHR{:}CHR' \longrightarrow \cdot CHR\cdot CHR'X\ (I) \text{ or } CHXR\cdot CHR'\cdot\ (II) \quad . \quad . \quad . \quad (1)$$

$$(I) + XY \longrightarrow CHYR\cdot CHR'X + X\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or

$$(II) + XY \longrightarrow CHXR\cdot CHR'Y + X\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This paper reports a study of some homolytic additions to crotonic acid and its ethyl ester, ethyl hydrogen maleate, ethyl β-acetylacrylate, ethyl cinnamate, and *cis*- and *trans*-cinnamonitrile.

In the above chain mechanism, no addition takes place if the initiating reaction (1) fails. On the other hand, if the propagation step (2) is slow, the intermediate radical (I) or (II) might (*a*) react with the olefin to form telomers, or (*b*), at higher concentration, undergo chain termination by disproportionation or dimerisation. Such side reactions might obscure the main course of the reaction. Since a yield of over 50% is essential for a reliable evaluation of the stabilising influence of the competing groups, the choice of the reagent XY is critical. The substances which are known to add to olefins and have been well investigated are the polyhalogenated methanes, aliphatic aldehydes and α-bromo-esters (for a review, see Cadogan and Hey [6]). Of these, bromotrichloromethane (the initiating radical being $Cl_3C\cdot$) was chosen as the only readily available reagent for such reactions for

[1] Huang and Lee, *J.*, 1954, 2570.
[2] Kharasch, Schwartz, and Nudenberg, *J. Org. Chem.*, 1953, **18**, 337.
[3] Kharasch, McBay, and Urry, *J. Amer. Chem. Soc.*, 1948, **70**, 1269.
[4] Huang, *J.*, 1954, 3084.
[5] Haszeldine, *J.*, 1953, 3565.
[6] Cadogan and Hey, *Quart. Rev.*, 1954, **8**, 308; cf. Kharasch, Skell, and Fisher, *J. Amer. Chem. Soc.*, 1948, **70**, 1055.

nearly all olefins, even styrene.[7] Aliphatic aldehydes, especially butanal, add well to certain olefins, but in some cases lead to formation of telomers, *e.g.*, with ethyl fumarate,[8] and in others do not add at all, notably to substances in which the olefinic double bond is conjugated with a benzene ring, as in benzylideneacetone.[9] Where applicable, however, the use of butanal is convenient, in that the structures of the resulting adducts can often be easily elucidated. Both these reagents have therefore been employed, with benzoyl peroxide as the catalyst.

Addition of bromotrichloromethane to ethyl crotonate gave the ester (III) in 84% yield. This was converted smoothly, by potassium acetate in hot acetic acid or by potassium hydroxide in cold ethanol, into the butenoate (IV), which in turn, with concentrated sulphuric acid, gave mesaconic acid. Thus the adduct has structure (III) and not the alternative (III*a*). Since the intermediate radical (V) was clearly involved, ethoxycarbonyl is more stabilising than methyl.

$$\underset{\text{(III)}}{\text{Me·CH(Br)·CH(CCl}_3\text{)·CO}_2\text{Et}} \qquad \underset{\text{(III}a\text{)}}{\text{Me·CH(CCl}_3\text{)·CH(Br)·CO}_2\text{Et}} \qquad \underset{\text{(IV)}}{\text{Me·C(CCl}_3\text{)=CH·CO}_2\text{Et}}$$

$$\underset{\text{(V)}}{\text{Me·CH·CH(CCl}_3\text{)·CO}_2\text{Et}} \qquad \underset{\text{(VI)}}{\text{Pr·CO·CHMe·CH}_2\text{·CO}_2\text{Et}}$$

Addition of butanal to the same ester afforded a 77% yield of the γ-keto-ester (VI) which on hydrolysis furnished the corresponding keto-acid. The identity of the adduct is hence beyond doubt, since the alternative mode of addition would have led to a β-keto-ester, which would have been decarboxylated on hydrolysis. This result confirms the previous finding.

Addition of butanal to crotonic acid led to an excellent yield (83%) of the same γ-keto-acid. The carboxyl group is therefore a more effective stabilising group than methyl. It is of interest to note the isolation in the neutral fraction of the product of small quantities of butyroin, formed probably by the action of the butyryl radical on butanal. The formation of acetoin by ultraviolet irradiation of acetaldehyde and of pyruvic acid [10] probably proceeds by a similar mechanism.

The products of addition of butanal to ethyl hydrogen maleate were separated into a neutral and an acid fraction. The former and main fraction consisted chiefly of ethyl 4-oxoheptanoate (49% overall yield) which in all probability was formed by decarboxylation of the β-keto-acid (VII), derived in turn *via* an initial radical addition to the carbon atom adjacent to the carboxyl group in ethyl hydrogen maleate. (It is not known whether decarboxylation occurred with the intermediate radical or the final addition product.) The acidic fraction was a mixture from which were isolated, after alkaline hydrolysis, small quantities of 4-oxoheptanoic acid. This could be obtained by the hydrolysis and partial decarboxylation of the alternative adduct (VIII). Since the adduct (VII) appears to be the main product it is reasonable to conclude that the ester group is more stabilising than the acid group.

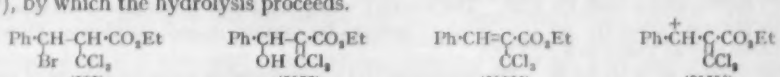
$$\underset{\text{(VII)}}{\text{Pr·CO·CH(CH}_2\text{·CO}_2\text{Et)·CO}_2\text{H}} \qquad \underset{\text{(VIII)}}{\text{Pr·CO·CH(CH}_2\text{·CO}_2\text{H)·CO}_2\text{Et}} \qquad \underset{\text{(IX)}}{\text{Me·CO·CH}_2\text{·CH(COPr)·CO}_2\text{Et}} \qquad \underset{\text{(X)}}{\text{Me·CO·CH}_2\text{·CH}_2\text{·COPr}}$$

Ethyl β-acetylacrylate and butanal gave an adduct (56% yield) which exhibited the usual properties of a keto-enol system and on hydrolysis with potassium carbonate suffered decarboxylation also, to give the diketone (X). The adduct must therefore be the β-keto-ester (IX), the formation of which indicates the greater stabilising influence of the ketonic group.

In ethyl cinnamate the steric factors might seem capable of assuming significant proportions. However, Fisher–Taylor–Hirschfelder models of the two possible adducts

[7] Kharasch, Simon, and Nudenberg, *J. Org. Chem.*, 1953, **18**, 328.
[8] Patrick, *ibid.*, 1952, **17**, 1009.
[9] *Idem*, *ibid.*, p. 1269.
[10] Dirscherl, *Z. physiol. Chem.*, 1938, **219**, 177.

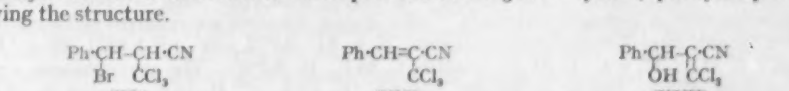
with bromotrichloromethane showed both molecules to be strainless and, since the addition does not involve a transition state with higher compression than the end-product, the steric picture can be discounted. Addition of bromotrichloromethane to ethyl cinnamate furnished a crystalline adduct (72% yield) which was converted by boiling aqueous-alcoholic potassium hydroxide into benzylidenemalonic acid. The structure of the adduct must therefore be (XI). Treatment with potasium hydroxide in cold ethanol, however, gave a partially dechlorinated neutral substance, probably (XII), formed presumably by partial hydrolysis during isolation of the allylic chloride (XIII). Hydrolysis of the product (XII) with acetic acid containing perchloric acid [7] also furnished benzylidenemalonic acid. This contrast in behaviour of (XIII) with the allyl trichloride (IV) may be attributed to the stabilising effect of the benzene ring on the intermediate carbonium ion (XIV), by which the hydrolysis proceeds.



(XI) (XII) (XIII) (XIV)

In view of Patrick's finding [9] that butanal does not add to benzylideneacetone, its addition to ethyl cinnamate was not carried out. An attempt to add ethyl bromoacetate, however, proved unsuccessful.

Addition of bromotrichloromethane to *cis*-cinnamonitrile gave, again in satisfactory yield, an adduct shown by degradation to be (XV). Isolation by crystallisation or distillation not proving feasible, the adduct was dehydrobrominated with potassium acetate in acetic acid, and was thereby obtained, not as the allyl trichloride (XVI), but as the partially hydrolysed (XVII) in a 56% overall yield calculated on the nitrile consumed. Hydrolysis of this with acetic acid and perchloric acid gave α-cyano-β-phenylacrylic acid, proving the structure.



(XV) (XVI) (XVII)

The same product (XVII) was obtained from *trans*-cinnamonitrile. However, the yield was considerably lower (33%), while the weight ratio between undistillable material and the adduct formed (approx. 1 : 1) was much increased (for the *cis*-nitrile the ratio was 1 : 2·2). Inasmuch as the same intermediate free radical is involved with both isomers, the high proportion of polymer in one case must be attributed, not to dimerisation of this intermediate radical, but to the formation of telomers as a result of different degrees of susceptibility of the isomeric nitriles towards attack by the same radical. This result is in contrast with those for ethyl crotonate and cinnamate, both of which are also ***trans***, but parallels the addition of butanal to ethyl maleate and fumarate.[8]

Again in contrast with ethyl crotonate and cinnamate, more than 50% of either cinnamonitrile did not enter reaction, even though higher molar ratios of bromotrichloromethane and of the catalyst were employed for a longer reaction time. In view of the absence of hexachloroethane in the products, this indicates a short chain length rather than an inefficient initiating reaction.

The relative stabilising influence of the substituents so far studied are thus: Ph > CO_2Et, CN; CO > CO_2Et > CO_2H > Me.

Experimental

Addition of Bromotrichloromethane to Ethyl Crotonate.—A mixture of ethyl crotonate (20 g., 0·17 mole) and bromotrichloromethane (140 g., 0·70 mole) was heated at 80° under nitrogen while benzoyl peroxide (3·6 g., 0·015 mole) was added in 4 portions during 6 hr., the mixture being then further heated for 2 hr. On cooling, ether was added, and the solution extracted 4 times with 10% aqueous sodium hydrogen carbonate, to remove benzoic acid. After drying, the ether was removed, and the unchanged bromotrichloromethane (*ca.* 90 g.) recovered by distillation under a partial vacuum. Distillation of the residue then gave *ethyl 2-bromo-3-trichloromethylbutanoate*, b. p. 88—92°/1 mm. (46 g., 84%), and a yellow residue (7 g.). Redistillation of the

main product gave a colourless liquid, b. p. 92—93°/1 mm., n_D^{22} 1·5007 (Found: C, 27·3; H, 3·5; Cl, 34·5. $C_7H_{10}O_2BrCl_3$ requires C, 26·9; H, 3·2; Cl, 34·1%).

Dehydrobromination.—(*a*) The above adduct (6·0 g., 0·02 mole) in cold absolute ethanol (5 c.c.) was added to a solution of potassium hydroxide (1·15 g., 0·02 mole) in the same solvent (15 c.c.). A white precipitate separated almost immediately and the mixture warmed slightly. After 2·5 hr. at room temperature (28°) a few drops of acetic acid were added, the solid (potassium bromide) was filtered off, and the filtrate concentrated to *ca.* 3 c.c. Aqueous sodium carbonate (10%) was added and the product extracted into ether, washed with water, dried, and concentrated. Distillation then gave *ethyl 3-trichloromethylbut-2-enoate*, b. p. 66—68°/1 mm., n_D^{22} 1·4912 (3·1 g., 66%) (Found: C, 36·7; H, 4·1; Br, 0. $C_7H_9O_2Cl_3$ requires C, 36·3; H, 3·9%).

(*b*) The above adduct (10·4 g.) was heated with potassium acetate (10 g.) and acetic acid (50 c.c.) on the steam-bath for 6 hr. The mixture was poured into water and neutralised with aqueous sodium carbonate, and the product isolated by extraction and distillation, giving the same butenoate as above (5·6 g., 73%).

Hydrolysis to mesaconic acid. The butenoate (1·3 g.), dissolved in twice its volume of concentrated sulphuric acid, was kept at room temperature for 24 hr., after which the solution was heated at 80° for 2 hr. It was then poured on ice (15 g.) and extracted with benzene (2 × 15 c.c.) and then with ether (5 × 15 c.c.). The ethereal extract, after being dried, was concentrated, giving mesaconic acid which, crystallised from ethanol–benzene, had m. p. 202° (lit., 202—204°) (0·15 g., 20%) (Found: C, 46·2; H, 4·75. Calc. for $C_5H_6O_4$: C, 46·2; H, 4·65%). Lower yields were obtained when heating was omitted or extended to 4 hr.

Addition of Butanal to Ethyl Crotonate.—Ethyl crotonate (23 g., 0·20 mole) and butanal (86 g., 1·2 moles) were heated at 80° under reflux in an atmosphere of nitrogen while benzoyl peroxide (3·7 g., 0·016 mole) was added in 4 portions during 6 hr. After 3 more hours' heating the excess of butanal was distilled off on the steam-bath, the last traces being removed by co-distillation with benzene. The residue was diluted with ether and extracted repeatedly with aqueous sodium hydrogen carbonate. After drying, the ether was removed and the product distilled, giving *ethyl 3-methyl-4-oxoheptanoate*, b. p. 81—83°/2 mm., n_D^{22} 1·4271 (29 g., 77%) (Found: C, 64·2; H, 9·9. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). The *semicarbazone*, needles from aqueous ethanol, had m. p. 96—97° (Found: N, 17·3. $C_{11}H_{21}O_3N_3$ requires N, 17·3%). The keto-ester was unaffected by a boiling 10% solution of potassium carbonate in 80% aqueous ethanol for 6 hr.

This ester (9·0 g.) was boiled with 5% aqueous sodium hydroxide (70 c.c.) for 3·5 hr. by which time the mixture had become homogeneous. It was cooled and extracted twice with ether, then acidified with dilute sulphuric acid, and the acid was taken up in ether, dried, and distilled, giving *3-methyl-4-oxoheptanoic acid*, b. p. 126°/3 mm., n_D^{22} 1·4414 (6·2 g.) (Found: C, 61·1; H, 9·0. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%). The *semicarbazone*, recrystallised from 90% ethanol, had m. p. 176—178° (Found: N, 19·8. $C_9H_{17}O_3N_3$ requires N, 19·5%).

Addition of Butanal to Crotonic acid.—Benzoyl peroxide (1·9 g., 0·008 mole) was decomposed in a solution of crotonic acid (8·0 g., 0·09 mole) in butanal (40 g., 0·56 mole) at 80° in the usual way. After removal of unused butanal, ether was added, and the acidic product taken up in 20% aqueous sodium carbonate (4 × 40 c.c.) which was washed twice with ether, acidified with 5N-sulphuric acid, and extracted with ether (4 × 60 c.c.). This extract was washed with water, dried, and distilled, to give 3-methyl-4-oxoheptanoic acid, b. p. 90—92°/0·5 mm. (12·6 g.), contaminated probably with benzoic acid. A sample (1·01 g.) of the distillate gave a good yield (1·12 g.) of the semicarbazone, m. p. 175°, alone or mixed with that obtained in the previous experiment. By comparison with the yield of semicarbazone obtained from a pure sample of the keto-acid under identical conditions, the above distillate was estimated to contain *ca.* 94% of the keto-acid. The yield was therefore 83%.

The neutral fraction remaining in the ethereal solution after alkali-extraction was concentrated and distilled, giving a fraction, b. p. 71—80°/1 mm., n_D^{22} 1·4295 (1·9 g.), and a viscous residue (2 g.). The former was further distilled evaporatively, giving a colourless liquid, n_D^{22} 1·4269 (Found: C, 67·0; H, 11·2. Calc. for butyroin, $C_8H_{16}O_2$: C, 66·6; H, 11·2%). Corson Benson, and Goodwin [11] report, for butyroin, b. p. 80—82°/10 mm., n_D^{26} 1·4242. When warmed with Brady's reagent it readily formed *octane-3 : 4-dione bis-2 : 4-dinitrophenylhydrazone* which crystallised from ethanol in needles, m. p. 109—110° (Found: C, 47·7; H, 4·8; N, 21·9. $C_{20}H_{22}O_8N_8$ requires C, 47·8; H, 4·4; N, 22·3%).

[11] Corson, Benson, and Goodwin, *J. Amer. Chem. Soc.*, 1930, **52**, 3988.

Addition of Butanal to Ethyl Hydrogen Maleate.—Ethyl hydrogen maleate, prepared by Shields's method [12] in 8% yield, had b. p. 110°/1 mm., n_D^{22} 1·4590 (Found: C, 50·4; H, 5·9. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·6%).

The product from ethyl hydrogen maleate (7·0 g., 0·05 mole), butanal (22 g., 0·3 mole), and benzoyl peroxide (2·0 g., 0·008 mole) was dissolved in ether, and separated by extraction with 10% aqueous sodium hydrogen carbonate (5 × 20 c.c.) into a neutral and an acidic fraction. The neutral fraction (7·4 g.) was distilled, giving mainly *ethyl 4-oxoheptanoate*, b. p. 50—54°/1 mm., n_D^{22} 1·4278 (4·0 g., 49%) (Found: C, 63·2; H, 9·55. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%), whose *semicarbazone*, needles from aqueous ethanol, had m. p. 107—109° (Found: N, 18·4. $C_{10}H_{19}O_3N_3$ requires N, 18·3%). Hydrolysis by boiling 10% aqueous sodium hydroxide for 3 hr. gave a good yield of the keto-acid, m. p. 46—46·5° (lit., m. p. 47—48°), which formed a *semicarbazone*, m. p. 150—152° (from aqueous ethanol) (Found: N, 20·8. $C_8H_{15}O_3N_3$ requires N, 20·9%). The keto-acid and its methyl ester have been reported by Ladd.[13] The residue (2·8 g.) from the above distillation was further distilled, giving two small fractions of varying refractive indices, b. p. 110—120° (bath)/0·5 mm. (total 1·1 g.) (which gave very small quantities of solid derivatives with Brady's reagent and with semicarbazide), and an undistillable residue (1·3 g.), all of which were not further investigated.

The hydrogen carbonate extract was acidified with 5N-sulphuric acid and extracted with ether, dried, and concentrated to a viscous liquid. A solid (0·8 g.) which separated crystallised from light petroleum; it was benzoic acid (m. p. and mixed m. p.), more of which (0·9 g.) sublimed on subsequent heating of the liquid at 0·5 mm. The residual liquid (2·7 g.) was divided into portions A and B. A (1·7 g.) was distilled, giving a colourless liquid, b. p. 120—135° (bath)/0·5 mm. (0·48 g.), which did not exhibit ketonic properties. The portion B (1·0 g.) was dissolved in 10% aqueous potassium hydroxide (10 c.c.), kept for 20 hr. at room temperature, then heated at 100° for 1 hr. The solution was acidified with sulphuric acid, extracted with ether, dried, and evaporated to a viscous oil. This gave 4-ketoheptanoic acid semicarbazone (0·09 g.), m. p. 149—150°, alone or mixed with the specimen obtained previously. To estimate the approximate amount of the keto-acid present in the mixture, an authentic sample was treated with semicarbazide under comparable conditions and the yields were compared. It was thus estimated that a total of 0·27 g. of 4-oxoheptanoic acid would be obtained by hydrolysis of the whole acidic fraction, corresponding to 0·32 g. or 3·3% of 2-ethoxycarbonyl-4-oxoheptanoic acid.

Addition of Butanal to Ethyl β-Acetylacrylate.—The acrylate, prepared from ethyl lævulate by bromination at 0° in ether solution followed by dehydrobromination with potassium acetate in acetic acid at 100°, had b. p. 48—50°/1 mm., n_D^{22} 1·4460 (cf. Wolff [14]). After being heated at 70° for 12 hr. with butanal (43 g., 0·6 mole) and benzoyl peroxide (2·4 g., 0·01 mole), the acrylate (14 g. 0·1 mole) gave, on distillation, (i) unchanged acrylate (2·5 g.), (ii) *ethyl 2 : 5-dioxo-octane-4-carboxylate*, b. p. 89—92°/0·5 mm., n_D^{22} 1·4445 (9·2 g., 54%) (Found: C, 62·0; H, 8·4; O, 30·0. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5; O, 29·9%), and (iii) a yellowish residue, which did not distil at 150° (bath)/0·5 mm. (6 g.). This adduct was soluble in 30% aqueous sodium hydroxide, gave a violet colour with ferric chloride, and decolorised bromine instantly in chloroform. (The starting material did not exhibit the first two properties, and decolorised bromine relatively slowly.) When treated with aqueous-alcoholic semicarbazide (with sodium acetate) at 80° or in the cold the adduct reacted with elimination of two mols. of water, to give in good yield a solid *derivative*, probably a pyrrole derivative (cf. reaction of acetonylacetone with oxalyl dihydrazide [15]) which crystallised from ethanol in needles, m. p. 238° (Found: C, 57·3; H, 7·7; N, 16·45. $C_{12}H_{19}O_2N_3$ requires C, 56·9; H, 7·6; N, 16·6%).

Hydrolysis and decarboxylation. The above product (3·5 g.) was heated under reflux with potassium carbonate (3·5 g.) in water (15 c.c.) and ethanol (10 c.c.) for 6 hr. The ethanol was removed under a partial vacuum, and the product extracted into ether, washed once with a little water, dried, and concentrated. Distillation gave *octane-2 : 5-dione*, a hygroscopic liquid, b. p. 60° (bath)/0·5 mm. or 105° (bath)/15 mm., n_D^{23} 1·4317 (1·4 g., 61%) (Found: C, 67·8, 67·4; H, 9·7, 10·3. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). This reacted with semicarbazide, with elimination of two mols. of water, to form a solid *derivative*, m. p. 172°, which crystallised from ethanol in needles (Found: C, 59·5; H, 8·15; N, 23·0. $C_9H_{15}ON_3$ requires C, 59·6; H, 8·3; N, 23·2%).

Addition of Bromotrichloromethane to Ethyl Cinnamate.—Ethyl cinnamate (35 g., 0·2 mole),

[12] Shields, *J.*, 1891, **59**, 736.
[13] Ladd and U. S. Rubber Co., U.S.P. 2,577,133/1951; B.P. 636,287/1950.
[14] Wolff, *Annalen*, 1891, **264**, 248.
[15] Bülow, *Ber.*, 1905, **38**, 3914.

bromotrichloromethane (160 g., 0·8 mole), and benzoyl peroxide (4 g., 0·016 mole) gave, after removal of benzoic acid, unchanged bromotrichloromethane, ethyl cinnamate (14 g.) (bath highest at 140°/0·2 mm.), and a yellow viscous liquid (40 g.) which on treatment with chilled methanol deposited *ethyl β-bromo-β-phenyl-α-trichloromethylpropionate*, m. p. 56—60° (23 g.), which crystallised from methanol in pale yellow prisms, m. p. 65·5° (Found: C, 38·9; H, 3·5; O, 8·6; Cl, 28·2. $C_{12}H_{12}O_2BrCl_3$ requires C, 38·5; H, 3·2; O, 8·5; Cl, 28·4%). The filtrate was concentrated to a pale yellow oil (16 g.), a portion of which (4 g.) on treatment with cold alcoholic potassium hydroxide as for the solid [see (*b*) below] gave the same product, b. p. 135° (bath)/1 mm., n_D^{23} 1·5330 (1·7 g.), showing that this oil contained approx. 60% by weight of the above solid. The total yield was therefore approx. 72%, calculated on the ester consumed.

When a six-mol. excess of the halogenated methane and 12 mole% of benzoyl peroxide were used very little ethyl cinnamate was recovered, but the yield of adduct was not appreciably increased.

Dehydrobromination and hydrolysis. (*a*) The above adduct (1·4 g.) in absolute ethanol (10 c.c.) was added to a solution of potassium hydroxide (2·8 g.) in the same solvent (30 c.c.). The mixture was kept at room temperature for 2 hr., then refluxed for 4 hr. Water was added, and the ethanol removed under a partial vacuum, this being repeated, and the residual aqueous solution (15 c.c.) was then washed with ether three times and acidified with 5N-sulphuric acid. The precipitated acid was taken up in much ether. Removal of the ether gave a solid, which after recrystallisation from benzene–*cyclo*hexane, melted with efflorescence at 185° (115 mg., 16% overall), raised to 196—199° on further crystallisation (Found: C, 62·0; H, 4·3. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). A sample (2 mg.) after being heated at 200° for 1 min., cooled, and recrystallised from aqueous ethanol gave cinnamic acid, m. p. and mixed m. p. 131—133°. Liebermann [16] reports benzylidenemalonic acid, m. p. 195—196°, decomposing to cinnamic acid when heated.

(*b*) The above adduct (3·7 g., 0·01 mole) in absolute ethanol was added to a solution of potassium hydroxide (0·62 g., 0·011 mole) in the same solvent (20 c.c.) with cooling. After 5 hr. at 28° a few drops of acetic acid were added, and most of the ethanol was removed on the steam-bath. Ether was added, and the solution was washed repeatedly with 5% sodium hydrogen carbonate solution, dried, and concentrated to an oil (2·9 g.). The hydrogen carbonate washings on acidification gave no appreciable quantities of acidic material. The oil on distillation gave *ethyl α-dichloromethylene-β-hydroxy-β-phenylpropionate*, b. p. 114°/0·5 mm., n_D^{22} 1·5332 (2 g.) (Found: C, 52·0; H, 4·6; Cl, 25·9; O, 16·9. $C_{12}H_{12}O_3Cl_2$ requires C, 52·5; H, 4·4; Cl, 25·8; O, 17·4%).

(*c*) The above adduct (1·2 g.) was heated with potassium acetate (0·8 g.) and acetic acid (12 c.c.) on the steam-bath for 7 hr. and the product isolated in the usual way, giving the same product (0·61 g.) as in (*b*).

Hydrolysis with perchloric acid. The product from (*b*) above (0·5 g.) was boiled gently with acetic acid (5 c.c.) and 60% perchloric acid (0·5 c.c.) for 4 hr. Most of the acetic acid was removed by distillation under a partial vacuum, water was added (*ca.* 10 c.c.), and distillation continued until about 1 c.c. of water remained. This was extracted with ether, and the acid taken up in sodium hydrogen carbonate, washed with ether, precipitated by acidification, and again taken up in much ether. Evaporation of the ether yielded benzylidenemalonic acid (27 mg.), m. p. and mixed m. p. 197—199°.

Addition of Bromotrichloromethane to cis- *and* trans-*Cinnamonitrile.*—*cis-* and *trans*-Cinnamonitrile were prepared by decarboxylation of α-cyano-β-phenylacrylic acid in pyridine.[17] Three fractional distillations gave *cis*-isomer, b. p. 88—89°/2 mm., n_D^{21} 1·5882, and *trans*-isomer, b. p. 97—98°/2 mm., n_D^{23} 1·5988. Kistiakowsky [18] reports *cis* n_D^{20} 1·5843, *trans* n_D^{20} 1·6031.

cis-Cinnamonitrile (14 g., 0·11 mole) and bromotrichloromethane (140 g., 0·7 mole) were heated at 70° while benzoyl peroxide (3·2 g., 0·013 mole) was added in six portions during 8 hr., the mixture being then heated for 4 hr. more. After removal of benzoic acid, distillation recovered unchanged bromotrichloromethane and cinnamonitrile (8·5 g.), leaving a residue (11 g.) which was used directly for the next operation. (In another experiment attempts to isolate the adduct by distillation and crystallisation were unsuccessful.)

The crude product from the above (6 g.) was heated with potassium acetate (3·5 g.) and acetic acid (30 c.c.) at 100° for 7 hr. The mixture was poured into water and neutralised with sodium hydrogen carbonate, then isolated in the usual manner. Distillation afforded fractions: (i)

[16] Liebermann, *Ber.*, 1893, **26**, 1572.
[17] Ghosez, *Bull. Soc. chim. belges*, 1932, **41**, 477.
[18] Kistiakowsky, *J. Amer. Chem. Soc.*, 1936, **58**, 2428.

b. p. 92—98°/1 mm. (0·8 g.); (ii) b. p. 105—120°/1 mm. (2·9 g., 56% overall yield, calc. on nitrile consumed); and (iii) an undistillable residue (1·3 g.). Fraction (ii) was further distilled, giving *α-dichloromethylene-β-hydroxy-β-phenylpropionitrile*, b. p. 110° (bath)/0·2 mm., n_D^{22} 1·5549 (Found: Cl, 31·1. $C_{10}H_7ONCl_2$ requires Cl, 31·1%).

The above propionitrile (0·35 g.) was gently boiled with acetic acid (2·5 c.c.) and 60% perchloric acid (0·3 c.c.) for 2·5 hr., and the product worked up in the usual way, giving α-cyano-β-phenylacrylic acid (0·115 g., 45%) which, crystallised from ethanol–benzene, had m. p. and mixed m. p. 181°. Prolonged heating (5 hr.) or use of a higher concentration of perchloric acid resulted in diminished yields.

Hydrolysis by a 10% solution of potassium hydroxide in refluxing 50% aqueous ethanol for 5 hr. gave a viscous oil.

trans-Cinnamonitrile gave the same propionitrile (33% yield), the identity being established by the boiling range, refractive index, analysis (Found: Cl, 31·1%), and hydrolysis with acetic–perchloric acid to α-cyano-β-phenylacrylic acid in approximately the same yield. The weight ratio of polymeric material : adduct obtained was higher than with *cis*-cinnamonitrile, being 1·5 : 1·6 and 1·7 : 1·5 in two experiments in which the dehydrobrominating agents were, respectively, potassium acetate in acetic acid, and potassium acetate in 90% ethanol. Dehydrobromination by methylaniline at 100° for 3 hr. gave on distillation a small yield of a product which became green. This method was therefore not investigated further.

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345. *The Isomerisation of Sulphidimines. Part III.* The Action of Chloramine-T on Cinnamyl Phenyl Sulphide, and the Hydrolysis and Oxidation of N-Substituted Toluene-p-Sulphonamides.*

By PETER A. BRISCOE, FREDERICK CHALLENGER, and PETER S. DUCKWORTH.

When cinnamyl phenyl sulphide and chloramine-T interact the sulphidimine† cannot be isolated, but immediately isomerises to *N*-1-phenylallyl-*N*-phenylthiotoluene-*p*-sulphonamide. The structure of this isomer follows from its alkaline hydrolysis to thiophenol and *N*-1-phenylallyltoluene-*p*-sulphonamide, identified by reduction to *N*-1-phenylpropyltoluene-*p*-sulphonamide. The isomerisation of the sulphidimine is therefore accompanied by inversion. The hydrolysis of several *N*-aralkyltoluene-*p*-sulphonamides with hydrochloric acid gives toluene-*p*-sulphonamide; the *N*-1-phenylethyl compound yields also styrene and 1-phenylethyl chloride. *N-iso*Propyltoluene-*p*-sulphonamide is almost unchanged, under comparable conditions, but the *tert.*-butyl derivative gives *tert.*-butyl chloride, *iso*butene, and toluene-*p*-sulphonamide. Oxidation of the *N-tert.*-butyl compound gives *N-tert.*-butyl-*p*-sulphamylbenzoic acid, *tert.*-butylamine, and 2-methyl-2-nitropropane. The mechanism of these reactions is discussed.

IN Parts I and II* it was shown that the sulphidimines prepared from diallyl sulphide‡ and either *N*-chloro-*N*-sodiotoluene-*p*-sulphonamide (chloramine-T) or *N*-chloro-4-methyl-3-nitro-*N*-sodiobenzenesulphonamide undergo spontaneous isomerisation at room temperature, an allyl group migrating to nitrogen. The isomers have the structure $CH_2{:}CH{\cdot}CH_2{\cdot}N(S{\cdot}CH_2{\cdot}CH{:}CH_2){\cdot}SO_2R$ because on boiling with alkali, $R{\cdot}SO_2{\cdot}NH{\cdot}CH_2{\cdot}CH{:}CH_2$, diallyl disulphide, hydrogen sulphide, and a resin arising from

* Part I, Ash, Challenger, and Greenwood, *J.*, 1951, 1877; Part II, Ash and Challenger, *J.*, 1952, 2792.

† Compounds of the type $\frac{R}{R'}{>}S{:}N{\cdot}SO_2{\cdot}C_6H_4Me\text{-}p$ were named sulphilimines by Mann and Pope (*J.*, 1922, **121**, 1052) and this term has been used in Parts I and II. The modern nomenclature is *SS*-dialkyl-*N*-toluene-*p*-sulphonylsulphidimines (Editorial Report on Nomenclature, *J.*, 1952, 5058).

‡ The analyses recorded (*J.*, 1950, 29; 1951, 1879) for the sulphidimine from diallyl sulphide were performed on the liquid, isomerised product and not on the original, unstable sulphidimine. The isomerisation was shown to occur without loss in weight.

acraldehyde are produced. With *N*-chloro-*N*-sodionaphthalene-1-sulphonamide, the isomer is formed at once. Allyl benzyl sulphide and chloramine-T give a sulphidimine $(CH_2Ph)(CH_2{:}CH{\cdot}CH_2)S{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$ which changes immediately at its m. p., or in a few days at room temperature, giving, by migration of the allyl group, the solid isomer $CH_2{:}CH{\cdot}CH_2{\cdot}N(S{\cdot}CH_2Ph){\cdot}SO_2{\cdot}C_6H_4Me$.

The similar conversion of *N*-crotyl-*N*-methylaniline oxide into *N*-methyl-*N*-(1-methylallyloxy)aniline proceeds with inversion of the crotyl group.[1] These changes resemble the Claisen rearrangements.[2] Mumm and Möller[3] found that crotyl α-phenyliminobenzyl ether (I) formed *N*-1-methylallyl-*N*-phenylbenzamide (II) at 210°, showing that inversion as well as rearrangement had occurred. The corresponding isomer (III) also rearranged giving (IV):

$$\underset{\text{(I)}}{Ph{\cdot}C(:NPh){\cdot}O{\cdot}CH_2{\cdot}CH{:}CHMe} \longrightarrow \underset{\text{(II)}}{Ph{\cdot}CO{\cdot}NPh{\cdot}CHMe{\cdot}CH{:}CH_2}$$

$$\underset{\text{(III)}}{Ph{\cdot}C(:NPh){\cdot}O{\cdot}CHMe{\cdot}CH{:}CH_2} \longrightarrow \underset{\text{(IV)}}{Ph{\cdot}CO{\cdot}NPh{\cdot}CH_2{\cdot}CH{:}CHMe}$$

With the sulphidimine from cinnamyl phenyl sulphide it might be possible to detect inversion should migration take place. Bergmann[4] showed that the isomerisation of cinnamyl thiocyanate to the *iso*thiocyanate is not accompanied by inversion, though crotyl thiocyanate was found by Mumm and Richter[5] to give 1-methylallyl *iso*thiocyanate after 2—3 days at room temperature, inversion having occurred:

$$Me{\cdot}CH{:}CH{\cdot}CH_2{\cdot}S{\cdot}CN \longrightarrow CH_2{:}CH{\cdot}CHMe{\cdot}N{:}C{:}S$$

These authors suggested that the steric effect of the phenyl group might be responsible for the absence of inversion in the case of cinnamyl thiocyanate.

No sulphidimine (V) could be isolated from cinnamyl phenyl sulphide and chloramine-T in aqueous acetone at room temperature or at 0°. At room temperature, migration and inversion of the cinnamyl group occurred; thus:

$$\underset{\text{(V)}}{CHPh{:}CH{\cdot}CH_2{\cdot}SPh{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me} \longrightarrow \underset{\text{(VI)}}{Ph{\cdot}S{\cdot}N(CHPh{\cdot}CH{:}CH_2){\cdot}SO_2{\cdot}C_6H_4Me}$$

The structure of the product (VI) follows from its decomposition with aqueous sodium hydroxide, whereby thiophenol, diphenyl disulphide, and *N*-1-phenylallyltoluene-*p*-sulphonamide $CH_2{:}CH{\cdot}CHPh{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4Me$ (VII) were obtained. The synthesis of the sulphonamide (VII) from toluene-*p*-sulphonamide and 1-phenylallyl bromide was impossible since the action of phosphorus tribromide on 1-phenylallyl alcohol yields cinnamyl bromide.[6] It was therefore reduced catalytically to *N*-1-phenylpropyltoluene-*p*-sulphonamide which was synthesised from 1-phenylpropylamine and toluene-*p*-sulphonyl chloride. An attempt to prepare it from toluene-*p*-sulphonamide, sodium hydroxide, and 1-phenylpropyl bromide yielded only β-methylstyrene; this was also obtained by Errera[7] from 1-phenylpropyl chloride and alcoholic potassium hydroxide. In order further to confirm the structure of (VII) and the occurrence of inversion during spontaneous isomerisation of the sulphidimine, the isomeric *N*-cinnamyltoluene-*p*-sulphonamide was prepared from cinnamyl bromide, toluene-*p*-sulphonamide, and alcoholic potassium hydroxide. *NN*-Dicinnamyltoluene-*p*-sulphonamide was obtained as a by-product and was also formed from the monocinnamyl-compound with cinnamyl bromide and alcoholic sodium hydroxide. The monocinnamyl derivative was different from *N*-1-phenylallyltoluene-*p*-sulphonamide (VII).

To confirm the structure of the *N*-monocinnamyltoluene-*p*-sulphonamide and to

[1] Kleinschmidt and Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 1929.
[2] Claisen and Tietze, *Ber.*, 1925, **58**, 275; 1926, **59**, 2344; Hurd and Cohen, *J. Amer. Chem. Soc.*, 1931, **53**, 1917.
[3] Mumm and Möller, *Ber.*, 1937, **70**, 2214.
[4] Bergmann, *J.*, 1935, 1361.
[5] Mumm and Richter, *Ber.*, 1940, **73**, 843.
[6] Moureu and Gallagher, *Bull. Soc. chim. France*, 1921, **29**, 1009.
[7] Errera, *Gazzetta*, 1886, **16**, 323.

exclude the possibility of a three-carbon isomerisation during the interaction of cinnamyl bromide with toluene-*p*-sulphonamide, the cinnamyl derivative was reduced with hydrogen and palladium–charcoal. The product was identical with that obtained from 3-phenylpropylamine and toluene-*p*-sulphonyl chloride.

Phenyl 1-phenylpropyl sulphide was converted into the sulphone, but the sulphide's reaction with chloramine-T appears to be abnormal and is under investigation.

Acid Hydrolysis of Sulphonamides.—Hydrolysis of the various *N*-aralkyltoluene-*p*-sulphonamides might afford further proof of their structure by formation of an amine and toluene-*p*-sulphonic acid, as in the hydrolysis of the *N*-substituted arenesulphonamides obtained in Hinsberg's process for the separation of amines, in which, however, concentrated hydrochloric acid at 150—170° is usually employed. We found that hot aqueous hydrochloric acid (1 : 1) and *N*-cinnamyl-, *N*-1-phenylallyl-, and *N*-1-phenylpropyl-toluene-*p*-sulphonamides gave toluene-*p*-sulphonamide. Odours of the aralkyl chlorides were always present. The *N*-3-phenylpropyl derivative was not hydrolysed by the hot concentrated acid. *N*-Benzyltoluene-*p*-sulphonamide is completely stable to the boiling aqueous acid (1 : 1), and *N*-allyltoluene-*p*-sulphonamide was only very slowly attacked, giving unidentified products. The stability of the allyl–nitrogen bond was to be expected in view of the formation of *N*-allyl*iso*butylamine from *N*-allyl-*N*-*iso*butyltoluene-*p*-sulphonamide and hydrochloric acid at 130° [8] and the stability of the similar bond in *N*-allyl-*N*-allylthiotoluene-*p*-sulphonamide to hot hydrochloric acid.[9]

There are very few recorded instances of the elimination of a sulphonamide on hydrolysis of a *N*-substituted derivative: (1) arenesulphonyl derivatives of *S*-alkyl*iso*thioureas give the arenesulphonamide and alkanethiol with strong acids; [10] (2) tritoluene-*p*-sulphonylmelamine gives cyanuric acid and toluene-*p*-sulphonamide with ethanolic hydrogen chloride, though hot sulphuric acid gives melamine and the sulphonic acid; [11] (3) *N*-phenyl-*N*-vinyltoluene-*p*-sulphonamide with 50% sulphuric acid gives *N*-phenyltoluene-*p*-sulphonamide and acetaldehyde.[12] The first two cases are not closely related to the abnormal hydrolyses examined by us, and the third probably involves the hydration of the vinyl group, giving an unstable 1-hydroxyethylamino-grouping.

The fission of the N–C bond by acid, in the cases of *N*-cinnamyl- and *N*-1-phenylallyltoluene-*p*-sulphonamides is probably associated with the relatively high stability of the aralkenyl groups as mesomeric carbonium ions.[13] If the first step in acid hydrolysis of sulphonamides is a protonisation of the nitrogen atom, the resulting ammonium ion might decompose by the splitting off of such a carbonium ion, rather than by separation of the arenesulphonyl cation, which presumably occurs, under more vigorous conditions, during normal hydrolysis:

$$Ar\cdot SO_2\cdot NHR \xrightarrow{H^+} Ar\cdot SO_2\cdot \overset{+}{N}H_2R \xrightarrow[H_2O]{\text{normal}} Ar\cdot SO_2\cdot OH + R\cdot NH_2 + H^+$$

$$\Big\downarrow \text{abnormal}$$

$$Ar\cdot SO_2\cdot NH_2 + R^+$$

The carbonium ion, $Ph\cdot CH{:}CH\cdot \overset{+}{C}H_2 \longleftrightarrow Ph\cdot \overset{+}{C}H\cdot CH{:}CH_2$, can become stabilised either by capture of a chlorine ion, giving cinnamyl chloride, or by ejection of a proton, giving phenylallene; in either case, cationic polymerisation may follow.

The abnormal hydrolysis of *N*-1-phenylpropyltoluene-*p*-sulphonamide (see above) is explicable on similar lines, since there is evidence that 1-phenylalkyl groups have considerable stability as cations.[13] To confirm this view, *N*-1-phenylethyltoluene-*p*-sulphonamide was boiled with aqueous (1 : 1) hydrochloric acid. As expected, the products were toluene-*p*-sulphonamide, 1-phenylethyl chloride, and styrene. When hydrolysis was

[8] Wedekind, *Ber.*, 1909, **42**, 3941.
[9] Ash, Challenger, and Greenwood, *J.*, 1951, 1877.
[10] Bergmann, Israelashvili, and Weinberg, *J. Amer. Chem. Soc.*, 1946, **68**, 761.
[11] Kurzer and Powell, *J.*, 1953, 2536.
[12] Clemo and Perkin, *J.*, 1924, **125**, 1808.
[13] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 324, 586.

effected with phosphoric acid at 100°, the products were toluene-*p*-sulphonamide and an oily mixture of distyrene and higher polymers which was almost identical with the mixture of liquid polymers obtained from styrene and phosphoric acid [14] and from styrene and sulphuric acid.[15]

Ingold [16] points out that the stability of the 1-phenylethyl cation is comparable with that of trialkylmethyl cations. Hickinbottom's results [17] are relevant. He found that *N-tert.*-butyl-*N*-phenyltoluene-*p*-sulphonamide with 15N-sulphuric at 135—145° gave *N*-phenyltoluene-*p*-sulphonamide in 85% yield. *N-tert.*-Butyl-, *N-tert.*-pentyl-, and *N-tert.*-hexyl-anilines with strong acids at 110—145° slowly gave low yields of aniline.

The hydrolysis of *N-tert.*-butyltoluene-*p*-sulphonamide might therefore be expected to be abnormal and to give toluene-*p*-sulphonamide and reaction products of the *tert.*-butyl cation. We obtained the arenesulphonamide, *tert.*-butyl chloride, and *iso*butene. If the *tert.*-butyl chloride is continuously removed, little *iso*butene is produced, suggesting that the chloride is the primary product. In contrast, *N-iso*propyltoluene-*p*-sulphonamide was recovered in high yield after prolonged boiling with hydrochloric acid.

N-tert.-Butyltoluene-*p*-sulphonamide is almost insoluble in hot dilute alkali, in contrast with the solubility in cold alkali of most *N*-monoalkyl-sulphonamides, including the *N-iso*propyl compound. In this respect the *N-tert.*-butyl compound resembles *N*-benzylbenzenesulphonamide and *N*-benzyltoluene-*p*-sulphonamide.[18] *N*-1-Phenylethyl-, *N*-cinnamyl-, *N*-1-phenylallyl-, and *N*-1-phenylpropyl-toluene-*p*-sulphonamide dissolve in hot aqueous sodium hydroxide, but separate again when the solution is cooled.

Oxidation of Sulphonamides.—In Part II it was shown that *N*-allyltoluene-*p*-sulphonamide is oxidised by excess of boiling alkaline permanganate to *p*-sulphamylbenzoic acid. This acid is also obtained with toluene-*p*-sulphonamide when the corresponding *N*-methyl and *N*-ethyl derivatives are similarly oxidised. We are aware of only one other recorded oxidative dealkylation of *N*-alkylsulphonamides. Verkade [19] found that *N-o*-methoxyphenyl-*N*-methyltoluene-*p*-sulphonamide gives *N*-2-methoxy-4-nitrophenyltoluene-*p*-sulphonamide with 10% nitric acid at 80°. Under milder conditions, however, the *N*-methyl-sulphonamido-group is not attacked. Remsen and Clark [20] prepared *o*-carboxy-*N*-methylbenzenesulphonamide from *N*-methyltoluene-*o*-sulphonamide and alkaline permanganate below 10°. Oxidative dealkylation of amines by permanganate has, however, been observed with tropine and scopoline,[21] and with dibutylamine.[22]

The oxidation of primary and secondary amines probably involves a preliminary dehydrogenation to the imine. This has been isolated from benzylaniline and its substitution products [23] and aminofluorene.[24] Usually, however, a carbonyl derivative is produced, presumably by hydrolysis of the imine.[25, 26] We have detected acetone, *p*-sulphamylbenzoic acid, and toluene-*p*-sulphonamide on permanganate oxidation of *N-iso*propyltoluene-*p*-sulphonamide in either neutral or alkaline solution. With limited quantities of permanganate, oxidation of the methyl group of the toluene-*p*-sulphonyl residue and of the *N*-alkyl group occurs simultaneously. Such dealkylations do not require the presence of a hydrogen atom on the nitrogen since *NN*-dimethyltoluene-*p*-sulphonamide is readily dealkylated by alkaline permanganate, giving *p*-sulphamylbenzoic acid. This reaction may be compared with the easy oxidation of tertiary amines.

Vorländer [27] and Goldschmidt and Beuschel [24] found that *tert.*-butylamine, which contains no hydrogen on the α-carbon atom, was not oxidised by permanganate under

[14] Cf. Dumontet, *Compt. rend.*, 1952, **234**, 1173.
[15] Risi and Gauvin, *Canad. J. Res.*, 1936, **14**, *B*, 255.
[16] Ingold, *op. cit.*, ref. 13, pp. 316, 325.
[17] Hickinbottom, *J.*, 1933, 1070.
[18] Carothers, Bickford, and Hurwitz, *J. Amer. Chem. Soc.*, 1927, **49**, 2913.
[19] Verkade, *Rec. Trav. chim.*, 1948, **67**, 241.
[20] Remsen and Clark, *Amer. Chem. J.*, 1903, **30**, 281.
[21] Houben-Weyl, " Die Methoden der Organischen Chemie," Thieme, Leipzig, 1925, Vol. II, p. 21.
[22] Smirnow and Shklyaruk, *J. Gen. Chem., U.S.S.R.*, 1950, **20**, 331 (*Chem. Abs.*, 1950, **44**, 3689).
[23] Ref. 21, p. 96.
[24] Goldschmidt and Beuschel, *Annalen*, 1926, **447**, 197.
[25] Wallach and Claisen, *Ber.*, 1875, **8**, 1237.
[26] Goldschmidt and Voeth, *Annalen*, 1924, **435**, 265.
[27] Vorländer, *ibid.*, 1906, **345**, 251.

conditions where other amines were rapidly oxidised. The behaviour of *N-tert.*-butyltoluene-*p*-sulphonamide towards alkaline permanganate was therefore examined. Under conditions (*A*) where other *N*-alkyltoluene-*p*-sulphonamides give approximately 50% yields of *p*-sulphamylbenzoic acid, the *N-tert.*-butyl compound gave in 68% yield *N-tert.*-butyl-*p*-sulphamylbenzoic acid free from any other sulphonamide or carboxylic acid. The minor products of the permanganate oxidation (*A*) were *tert.*-butylamine and 2-methyl-2-nitropropane. These compounds were also obtained with oxalic acid on prolonged oxidation (*B*) of *N-tert.*-butyl-*p*-sulphamylbenzoic acid. The nitro-compound was identical with a specimen prepared by permanganate oxidation of *tert.*-butylamine.[28] The 2-methyl-2-nitropropane produced in reactions (*A*) and (*B*) presumably arises by the same oxidation. It is, however, unlikely that *tert.*-butylamine is formed by simple alkaline hydrolysis of its toluene-*p*-sulphonyl or *p*-carboxybenzenesulphonyl derivatives because these compounds were almost completely unaffected by boiling 2N-sodium hydroxide.[29]

A second possible mechanism for reactions (*A*) and (*B*) would involve oxidation of the sulphonamide to a hydroxylamine derivative, p-$CO_2H{\cdot}C_6H_4{\cdot}SO_2{\cdot}N(OH)Bu^t$. Such compounds are hydrolysed by alkali to a nitroso-compound and a sulphinic acid thus:[30] $Ph{\cdot}SO_2{\cdot}N(OH)Ph + NaOH = Ph{\cdot}SO_2Na + Ph{\cdot}NO + H_2O$. The nitro-compound could presumably arise by oxidation of the nitroso-derivative, but this mechanism does not explain the formation of the amine which is also produced in reactions (*A*) and (*B*). Furthermore, the sulphinic acid should yield the sulphonic acid on further oxidation; *p*-sulphobenzoic acid could not be detected. Finally, the attachment of oxygen to amine nitrogen is particularly facilitated by such reagents as Caro's acid, benzoyl peroxide, and hydrogen peroxide.[26,31] *N-tert.*-Butyl-*p*-sulphamylbenzoic acid was unchanged after treatment with neutral sodium monopersulphate, ethereal monoperphthalic acid, hydrogen peroxide in acetic acid or in sodium hydroxide, or sodium peroxide. Caro's acid at 40° gave *p*-sulphamylbenzoic acid. The intermediate formation of a hydroxylamine derivative is therefore unlikely.

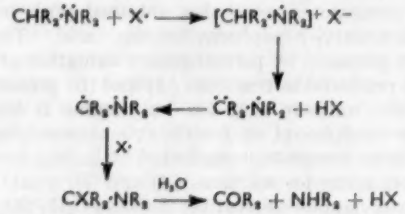
Probably, oxidative degradation of the aromatic ring gives oxalic acid (which was detected) and *tert.*-butylsulphamic acid. The literature contains very little clear information concerning the alkaline hydrolysis of *N*-alkylsulphamic acids. There is, however, some evidence that electron access to the nitrogen atom facilitates hydrolytic fission of the N–S link, phenylsulphamic acid being stable to hot strong alkali whereas the *p*-ethoxyphenyl compound readily gives *p*-phenetidine.[32] *tert.*-Butylsulphamic acid might therefore, under the conditions of our experiments, give *tert.*-butylamine and sulphate, both of which were detected. The amine would then yield 2-methyl-2-nitropropane on oxidation. The high consumption of permanganate (24 equiv. per mole) during the oxidation is also consistent with this assumption. Formation of oxalic acid and the other products mentioned above requires 26 equiv. Under identical conditions *p*-sulphamylbenzoic acid is slowly oxidised, giving oxalic acid and sulphate.

Analogy with *N-tert.*-butyltoluene-*p*-sulphonamide would suggest that toluene-*p*-sulphonanilide would be oxidised to *p*-carboxybenzenesulphonanilide and oxidation products of aniline. However, when an excess of 6% neutral or alkaline permanganate is used, the main product is *p*-sulphamylbenzoic acid, and we have not been able to detect nitrobenzene. With a limited quantity of 3% neutral ($MgSO_4$) permanganate, toluene-*p*-sulphonamide can be isolated, as reported by Troeger and Uhlmann.[33] These products must be formed by oxidative degradation of the *N*-phenyl ring. This degradation occurs far more rapidly with the sulphonanilide than with acetanilide.

No decision has yet been reached regarding the mechanism of oxidation of amines by alkaline permanganate. Drummond and Waters[34] consider that the first step is the removal of a single electron from the amine by the MnO_4^- ion and that attack occurs

[28] Kornblum and Clutter, *J. Amer. Chem. Soc.*, 1954, **76**, 4494.
[29] See also Sidgwick, "Organic Chemistry of Nitrogen," Univ. Press, Oxford, 1937, p. 157.
[30] Piloty, *Ber.*, 1896, **29**, 1559; Angeli, Angelico, and Scurti, *Chem. Zentr.*, 1902, II, 691.
[31] Ref. 29, p. 25.
[32] Audrieth *et al.*, *Chem. Rev.*, 1940, **26**, 68; Weil and Moser, *Ber.*, 1922, **55**, 732.
[33] Troeger and Uhlmann, *J. prakt. Chem.*, 1895, **51**, 435.
[34] Drummond and Waters, *J.*, 1953, 435.

vicinally to the nitrogen atom. Horner and Betzel [35] suggest that oxidation of tertiary amines by benzoyl peroxide also involves extraction of a single electron from the substrate, by means of a free radical. They suggest that this electron is removed from the unshared pair of the nitrogen atom and put forward the following scheme which might also apply to oxidation of tertiary amines or *N*-dialkylsulphonamides by permanganate (X· is a free radical) :



A slightly modified scheme could be suggested for oxidation of primary and secondary amines and of *N*-monoalkyl-sulphonamides. However, this mechanism would appear inapplicable to the oxidation of *N-tert.*-butyltoluene-*p*-sulphonamide. Removal of one electron from the nitrogen would give the radical-ion $[RSO_2\cdot\dot{N}H\cdot CMe_3]^+$, which might be expected to lose a proton giving $RSO_2\cdot\dot{N}\cdot CMe_3$. This free radical would then presumably dimerise to give the tetrasubstituted hydrazine $RSO_2\cdot N(CMe_3)\cdot N(CMe_3)\cdot SO_2R$.[24, 26] The oxidation products observed by us could hardly arise from further oxidation of such a hydrazine. To this extent our results support the conclusions of Drummond and Waters.[34]

Experimental

Preparation of Cinnamyl Phenyl Sulphide.—Cinnamyl bromide was prepared by a modification of Bouis's method [36] which yielded a purer product. Cinnamyl alcohol is added to phosphorus tribromide and pyridine in an ice-bath, and the cinnamyl bromide separated from phosphorus compounds by ether extraction followed by distillation; it had b. p. 127—129°/12 mm. (yield 74%). The method described by Tarbell and McCall [37] for the preparation of similar sulphides was then employed. Thiophenol (28·8 g.) was stirred into ethanolic sodium ethoxide [from sodium (6 g.) and ethanol (125 c.c.)]. Cinnamyl bromide (51·5 g.) was added slowly so as to keep the mixture warm but to avoid refluxing. After 3 hours' stirring the mixture was added to water (800 c.c.), and the precipitate crystallised from ethanol. It had m. p. 78·5° (yield, 47·2 g., 80%) (Found : C, 79·25, 79·25; H, 6·35, 6·15; S, 13·95, 14·15. Calc. for $C_{15}H_{14}S$: C, 79·65; H, 6·2; S, 14·15%). Barnard and Hargrave [38] prepared cinnamyl phenyl sulphide but gave no experimental details. Their sample had m. p. and mixed m. p. with the above specimen, 78°.

Dr. R. W. Saville, of the British Rubber Producers' Research Association, has determined the infrared spectrum of Barnard's sample and reports that : "The spectrum shows a band at 960 cm.$^{-1}$ indicating unsaturation of the type *trans*-R·CH:CHR. The band is not affected by conjugation, stilbene and other compounds with this type of unsaturation all showing the 960 cm.$^{-1}$ band. Vinylidene unsaturation $CH_2{=}C{:}$ is indicated by a band at 890 cm.$^{-1}$ and this band is not present in this case. Although, here, conjugation may alter the position of the 890 cm.$^{-1}$ band, it could not become as high as 960 cm.$^{-1}$. It appears that none of the isomer $CH_2{:}CH\cdot CHPh\cdot SPh$ is present, infrared evidence thus favouring the structure $Ph\cdot CH{:}CH\cdot CH_2\cdot SPh$." See also Bellamy.[39]

Cinnamyl Phenyl Sulphone.—Cinnamyl phenyl sulphide (2·5 g.) was dissolved in warm glacial acetic acid (40 c.c.). Hydrogen peroxide (30%; 1·6 c.c.) was then added, and the mixture gently warmed to keep the sulphide in solution, left at room temperature for 24 hr., and then poured into water (100 c.c.). Extraction with chloroform and washing with aqueous

[35] Horner and Betzel, *Annalen*, 1953, **579**, 175.
[36] Bouis, *Bull. Soc. chim. France*, 1927, **41**, 1160.
[37] Tarbell and McCall, *J. Amer. Chem. Soc.*, 1952, **74**, 48.
[38] Barnard and Hargrave, *Analyt. Chim. Acta*, 1951, **5**, 543.
[39] Bellamy, "Infra-Red Spectra of Complex Molecules," Methuen, London, 1954, p. 31.

sodium hydrogen carbonate and crystallisation from light petroleum containing 5% of chloroform yielded needles, m. p. 115° (Found: C, 70·2; H, 5·2; S, 12·4. Calc. for $C_{15}H_{14}O_3S$: C, 69·8; H, 5·4; S, 12·4%). Barnard [40] gives the m. p. of the sulphone as 112—112·5°.

Cinnamyl Phenyl Sulphide and Chloramine-T: Attempted Preparation of a Sulphidimine.—This reaction was carried out under various conditions: (1) in water alone, (2) in acetone containing different proportions of water at room temperature and at 0°, and (3) in boiling alcohol for 1 hr.; the yield of product was then very low. The best yield was obtained as follows: The sulphide (8 g.) in acetone (130 c.c.) was treated with chloramine-T (16 g.) in water (30 c.c.), and the mixture shaken for 1 hr. and poured into water (400 c.c.). The resulting white solid was separated, washed with water to remove chloramine-T, and with dilute sodium hydroxide to remove toluene-*p*-sulphonamide and finally with water. It was then dried and recrystallised from alcohol to constant m. p. 88° [yield 10·4 g., 71·5% calculated as the sulphidimine (V)]. The m. p. was unchanged after the substance had been kept for several months or recrystallised from a different solvent, or when kept at its m. p. for 3 hr. [Found: C, 66·6; H, 5·3; N, 3·5; S, 16·0%; *M* (camphor), 315. $C_{22}H_{21}O_2NS_2$ requires C, 66·85; H, 5·3; N, 3·55; S, 16·2%; *M*, 395].

When the sulphide and chloramine-T were stirred for 3 hr. at −10°, samples of solid removed at intervals and freed from toluene-*p*-sulphonamide with sodium hydroxide contained much unchanged sulphide.

Reactions of N-1-*Phenylallyl*-N-*phenylthiotoluene*-p-*sulphonamide* (VI), *m. p.* 88°.—(1) *With hydrochloric acid.* The compound (2 g.) was refluxed with the concentrated acid (25 c.c.) for 1½ hr., giving a yellow oil and a strong odour of cinnamyl chloride. On cooling, an oil (*A*) and a crystalline solid separated. After being washed with benzene the crystals melted at 138° alone or in admixture with toluene-*p*-sulphonamide, m. p. 138°. The benzene yielded an oil which gave an odour of benzaldehyde with hot acidified potassium permanganate. The oil (*A*) was washed with alkali, shaken with ether, and the extract washed with water and evaporated; the residue did not distil below 160°/22 mm. (cinnamyl chloride boils at 98°/18 mm.). The oil contained much chlorine and some nitrogen and sulphur and was probably mainly a polymer of cinnamyl chloride.

(2) *With sodium hydroxide.* The compound (VI) (2 g.) was refluxed for 2 hr. with aqueous 25% sodium hydroxide (10 c.c.), giving an oil which solidified on cooling. Several recrystallisations from aqueous methanol (1 : 1) gave crystals, m. p. 103°, of the *sulphonamide* (VII) (Found: C, 67·15; H, 5·95; N, 5·1; S, 11·1. $C_{16}H_{17}O_2NS$ requires C, 66·9; H, 5·9; N, 4·9; S, 11·15%).

The alkaline solution had an odour of thiophenol. Acidification gave an oil and intensified the odour. Lead acetate paper turned yellow, and a drop of mercuric cyanide gave a white precipitate when exposed to the vapour. Hydrogen sulphide was absent. The acid solution when kept for 24 hr. deposited a solid (0·2 g.) which after recrystallisation from ethanol had m. p. 62° alone and when mixed with authentic diphenyl disulphide.

(3) *Oxidation of the toluene*-p-*sulphonamide* (VI) *with alkaline potassium permanganate.* The compound (VI) (3 g.) was refluxed with water (15 c.c.), potassium permanganate (14 g.), and potassium carbonate (4 g.). The odour of benzaldehyde was detected. When no further reduction occurred, sulphur dioxide was passed in; the clear liquid contained some suspended solid (*S*) which was mainly diphenyl disulphide, m. p. and mixed m. p. 60°. Acidification of the filtrate gave a white solid, m. p. 280—283° (decomp.). The m. p. of *p*-sulphamylbenzoic acid is given in the literature as 280—281° (decomp.). One of us (P. A. B.) finds that crystallisation raises the m. p. to 292—293° (see p. 1766). In a second experiment steam distillation of the solid (*S*) yielded benzoic acid, m. p. and mixed m. p. 119—122°.

(4) *Reduction of the toluene*-p-*sulphonamide* (VI), *with zinc and hydrochloric acid.* The compound (VI) (1 g.) was mixed with successive quantities of zinc dust and the acid, a strong odour of thiophenol being produced. Solids were then separated and extracted with ether, yielding a white solid, m. p. 103—104° after recrystallisation from aqueous alcohol. An admixture with *N*-1-phenylallyltoluene-*p*-sulphonamide, m. p. 103°, had the same m. p. The m. p. of the *N*-cinnamyl-sulphonamide, m. p. 110°, was depressed to 80—90°. Reduction of compound (VI) (3 g.) with palladium gave an odour of thiophenol, much unchanged material, and a mixture which appeared to contain a small amount of *N*-1-phenylallyltoluene-*p*-sulphonamide.

Reactions of N-1-*Phenylallyltoluene*-p-*sulphonamide.*—Hydrolysis with hot 2N-sulphuric acid yielded a small amount of toluene-*p*-sulphonamide (m. p. and mixed m. p.); 1 g. of (VII) was boiled with syrupy phosphoric acid (1 c.c.) in diethylene glycol (2 c.c.) for 2 min., and the

[40] Barnard, personal communication.

product cooled, acidified with hydrochloric acid, and filtered, giving toluene-*p*-sulphonamide, m. p. and mixed m. p. 138°. The acid filtrate when made alkaline and extracted with ether did not yield amine. The *N*-1-phenylallyl compound was recovered unchanged after treatment in aqueous alcoholic suspension with sodium amalgam.

Hydrogenation of N-1-*Phenylallyltoluene*-p-*sulphonamide with 5% Palladium–Charcoal.*—The compound (VII) (2 g.) in ethanol (60 c.c.) with the catalyst (4·5 g.) absorbed 170 c.c. of hydrogen in 10 min. (Calc. for $C_{16}H_{17}O_2NS$[F] : 160 c.c.). Separation of the catalyst and concentration gave N-1-*phenylpropyltoluene*-p-*sulphonamide*, m. p. 108° after repeated crystallisation from aqueous ethanol.

The m. p. of a mixture with the phenylallyl compound (m. p. 103°) was 96—100° (Found : C, 66·35; H, 6·1. $C_{16}H_{19}O_2NS$ requires C, 66·4; H, 6·65; N, 4·85; S, 11·05%).

Synthesis of N-1-*Phenylpropyltoluene*-p-*sulphonamide.*—Propiophenone oxime, m. p. 54—55° (lit. 53—54°), was reduced with sodium and alcohol to 1-phenylpropylamine, b. p. 97·5°/30 mm. Billon [41] gives 100—105°/35 mm. The benzoyl derivative and the hydrochloride melted at 116—117° and 192°, respectively (lit. 115—116° and 194°). The base (2·8 g.), suspended in aqueous sodium hydroxide (50 c.c.), was added to toluene-*p*-sulphonyl chloride (4 g.) in the minimum quantity of acetone. The mixture was shaken for 10 min., the emulsion filtered, and the filtrate acidified and shaken. The precipitate (5·7 g., m. p. 103°) was recrystallised (aqueous ethanol) to m. p. 106—107° (Found : C, 66·45; H, 6·35; N, 5·15; S, 11·05%). The mixed m. p. with the product (m. p. 108°) of the previous experiment was 106—108°. An attempt to prepare this compound by refluxing toluene-*p*-sulphonamide (8·6 g.) and 1-phenylpropyl bromide (10 g.) in alcohol with alcoholic sodium hydroxide (2 g. in 80 c.c.) for 7 hr. yielded β-methylstyrene (b. p. 84—86°/25 mm.; lit. 76—78°/19 mm.) and unchanged sulphonamide.

Hydrolysis of N-1-*Phenylpropyltoluene*-p-*sulphonamide.*—The sulphonamide (0·5 g.) was refluxed with hydrochloric acid (60 c.c.) for 10 hr. A strong odour resembling that of 1-phenylpropyl bromide was produced, and on cooling, toluene-*p*-sulphonamide (0·1 g.; m. p. and mixed m. p. 136—138°) separated. The acid, when freed from oil, concentrated and made alkaline, gave no odour of an amine. Repetition of this experiment for 6 hr. with 1·5 g. of the sulphonamide gave the same result; some unchanged material was recovered, and amine not detected.

Hydrogenation of N-*Cinnamyltoluene*-p-*sulphonamide.*—The *N*-cinnamyl compound (2 g.) in ethanol (50 c.c.) in presence of palladium–charcoal catalyst (4 g.) absorbed 170 c.c. of hydrogen (Calc. : 160 c.c.). The filtered and evaporated solution left a solid, m. p. 66—67° [after crystallisation from aqueous methanol (1 : 1)] (Found : C, 66·2; H, 6·5; N, 4·75; S, 11·15. Calc. for $C_{16}H_{15}O_2NS$: C, 66·4; H, 6·65; N, 4·85; S, 11·1%). The mixed m. p. with an authentic sample of *N*-3-phenylpropyltoluene-*p*-sulphonamide, m. p. 66—67°, was the same.

Synthesis of N-3-*Phenylpropyltoluene*-p-*sulphonamide.*—3-Phenylpropylamine was prepared by Tafel's method.[42] About 0·5 g. was mixed with dilute sodium hydroxide (5 c.c.), and the mixture added to toluene-*p*-sulphonyl chloride in the minimum of acetone and shaken. After 30 min., hydrochloric acid (5 c.c.) was added to the emulsion. A brown oil separated which soon solidified to needles, m. p. 66—67° [after recrystallisation from aqueous methanol (1 : 1)]. Coke and McElvain [43] give m. p. 65·5°. The amide (0·4 g., prepared by hydrogenation, see above) was boiled with hydrochloric acid (20 c.c.) for 4 hr. Most of it was unchanged, and toluene-*p*-sulphonamide was not obtained.

N-*Mono-* and NN-*Di-cinnamyltoluene*-p-*sulphonamides.*—The following method is based on that of de Montmollin and Matile [44] for the preparation of the mono- and di-2-β-naphthyloxyethyl derivatives of toluene-*p*-sulphonamide. Cinnamyl bromide (5·9 g., 0·05 mole) and toluene-*p*-sulphonamide (8·6 g., 0·05 mole) in alcohol (60 c.c.) were treated with a solution of potassium hydroxide (2·9 g., 0·05 mole) in alcohol (25 c.c.) containing a few drops of water. The mixture was refluxed for 6 hr., the solvent removed, and water (100 c.c.) added. The resulting oily solid was washed with ether and shown to be unchanged sulphonamide. The ether was shaken with alkali to remove toluene-*p*-sulphonamide, then with water, and dried, yielding a yellow oil (6·6 g.), which was dissolved in methanol. Needles of NN-*dicinnamyl compound* separated, m. p. 95° (after recrystallisation from methanol) (Found : C, 74·45; H, 6·2; N, 4·65; S, 8·65. $C_{25}H_{23}O_2NS$ requires C, 74·45; H, 6·2; N, 4·65; S, 7·9%). Concentration of the methanol

[41] Billon, *Compt. rend.*, 1926, **182**, 472.
[42] Tafel, *Ber.*, 1886, **19**, 1930.
[43] Coke and McElvain, *J. Amer. Chem. Soc.*, 1931, **53**, 1589.
[44] de Montmollin and Matile, *Helv. Chim. Acta*, 1929, **12**, 871.

mother-liquors gave the *mono-derivative*, m. p. 110° (after recrystallisation from acetone–light petroleum) (Found: C, 66·8; H, 6·2; N, 4·65; S, 11·3. $C_{16}H_{17}O_2NS$ requires C, 66·9; H, 5·9; N, 4·9; S, 11·15%).

Conversion of the mono- into the di-cinnamyl derivative. The monocinnamyl compound (0·9 g.) was warmed with sodium hydroxide (0·18 g.) in ethanol (20 c.c.), cinnamyl bromide (0·6 g.) added, and the mixture refluxed for 3 hr. The solid which separated on cooling was washed with water. Recrystallisation from methanol gave the dicinnamyl compound, m. p. and mixed m. p. 92—95°.

Neither compound gave any odour with cold acidified potassium permanganate but, when warmed, benzaldehyde was detected in both cases. The di-derivative was insoluble in aqueous sodium hydroxide, hot or cold; the mono-derivative was insoluble in the cold but dissolved on being warmed and separated again on cooling. The monocinnamyl derivative (1 g.), when boiled for 7 hr. with diluted hydrochloric acid (1 : 1, 30 c.c.), gave an odour of cinnamyl chloride, and a deposit of toluene-*p*-sulphonamide on cooling. A black resin was also produced but the acid solution gave no amine odour when made alkaline.

Phenyl 1-Phenylpropyl Sulphide.—Thiophenol (2·9 g.) was added to a solution of sodium ethoxide [from sodium (0·6 g.) and ethanol (30 c.c.)], the mixture warmed, and 1-phenylpropyl bromide (5·75 g.) slowly added. After refluxing for 3 hr. the mixture was poured into water (500 c.c.), excess of alcohol removed, and the suspended oil extracted with ether and dried (Na_2SO_4). The *sulphide* distilled at 186—187°/25 mm., solidified on cooling, and after crystallisation from aqueous ethanol (1 : 1) formed needles, m. p. 42° (Found: C, 79·05; H, 7·0; S, 13·8. $C_{15}H_{16}S$ requires C, 78·9; H, 7·1; S, 14·05%).

Phenyl 1-Phenylpropyl Sulphone.—The sulphide (0·2 g.) in the minimum of glacial acetic acid was treated with 3% aqueous potassium permanganate in slight excess, sulphur dioxide passed in, and the colourless solution poured into water (100 c.c.). The resulting white *sulphone* (m. p. 94—97°) crystallised from ethanol in needles, m. p. 101° (Found: C, 68·95; H, 6·2; S, 12·4. $C_{15}H_{16}O_2S$ requires C, 69·2; H, 6·2; S, 12·3%).

Attempted Preparation of S-Phenyl-S-1-phenylpropyl-N-toluene-p-sulphonylsulphidimine.—Phenyl 1-phenylpropyl sulphide (3 g.) in acetone (30 c.c.) and chloramine-T (6 g.) in water (50 c.c.) were shaken together for 1 hr. and poured into water (250 c.c.). Evaporation of acetone left a wax which, after being washed with sodium hydroxide and then with water, had m. p. 99—111°; after repeated crystallisation from acetone–light petroleum the m. p. was finally raised to 116—117° (Found: C, 56·85; H, 4·60; N, 3·6; S, 23·05. $C_{13}H_{13}O_2NS_2$ requires C, 55·9; H, 4·7; N, 5·0; S, 22·95%). The *N-phenylthio-compound* will be studied in detail later. The aqueous filtrate from this reaction was extracted with ether, the resulting solid added to that from the mother-liquors of the compound, m. p. 116—117°, and the whole dissolved in acetone and shaken for 2 hr. with more chloramine-T in 20 c.c. of water. Distillation of the acetone left a solid which, after removal of toluene-*p*-sulphonamide with dilute sodium hydroxide, had m. p. 96—98° (0·1 g.).

The alkaline washings and the filtrates from the two treatments with chloramine-T were united and concentrated. A white solid (1·0 g.) separated; it had m. p. 228—229° after crystallisation from ethanol. A mixed m. p. with the sodium salt of *S*-phenyltoluene-*p*-sulphonamidosulphinetoluene-*p*-sulphonylimine, m. p. 231°, prepared by Clarke, Kenyon, and Phillips's method,[43] was 228—229°. Acidification gave the corresponding acid which was impure (m. p. 96—150°) after one crystallisation from alcohol (see below). Acidification of the alkaline filtrate from the salt of m. p. 228—229° gave toluene-*p*-sulphonamide.

Examination of the Residues from the Interaction of Chloramine-T and Cinnamyl Phenyl Sulphide.—After the identification of the compound (VI), m. p. 88°, arising from this reaction (see p. 1761) as *N*-1-phenylallyl-*N*-phenylthiotoluene-*p*-sulphonamide the aqueous acetone liquors were combined with the alkaline washings from the solid of m. p. 88° and concentrated to about two-thirds of their volume in an open dish on the steam-bath. A brown colour quickly developed and traces of solid formed. The alkaline solution (S) on extraction with ether yielded a brown oil with a strong odour of cinnamaldehyde and white crystals. The crystals were drained and washed with ethanol. They melted at 102—103° alone and in admixture with *N*-1-phenylallyltoluene-*p*-sulphonamide, m. p. 103°. The alkaline solution (S) was acidified with hydrochloric acid, and odours of cinnamyl chloride and thiophenol were detected. Extraction with ether yielded a brown solid which dissolved almost completely in warm dilute sodium hydroxide, but was mostly deposited on cooling; after two crystallisations from acetone–light petroleum it had 228—230° alone and in admixture with the sodium salt, m. p. 231° (see

[43] Clarke, Kenyon, and Phillips, *J.*, 1930, 1230.

above). Acidification of the alkaline extract gave a slight odour of thiophenol and a precipitate of toluene-*p*-sulphonamide, m. p. and mixed m. p. 137°.

N-tert.-*Butyltoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonyl chloride (57·2 g., 0·3 mole) in pyridine (70 c.c.) was added during 25 min. to a stirred solution of *tert.*-butylamine (21·9 g., 0·3 mole) in pyridine (25 c.c.). The temperature was kept at 35—40°. After 30 min. on the steam-bath, followed by addition of ice, the mixture was diluted to 1200 c.c. with water, and the precipitated solid was washed with dilute hydrochloric acid and water. Two crystallisations from aqueous ethanol (1 : 1) (charcoal) gave short white needles, sintering at 111°, m. p. 113—114° (Found : C, 58·1; H, 7·3; N, 6·2; S, 14·1. $C_{11}H_{17}O_2NS$ requires C, 58·1; H, 7·5; N, 6·2; S, 14·1%). The *sulphonamide* is sparingly soluble (less than 2%) in boiling 2N-sodium hydroxide, but soluble in a cold ethanol–water (5 : 3) solution of sodium hydroxide.

Hydrolysis of N-tert.-*butyltoluene*-p-*sulphonamide*. (1) Aqueous hydrochloric acid (1 : 1; 50 c.c.) and the sulphonamide (12·0 g.) were refluxed, and volatile matter escaping from the water-cooled condenser was collected in a trap cooled in methanol–solid carbon dioxide. The sulphonamide quickly melted, and after 10 min. the gases escaping from the condenser decolorised bromine in carbon tetrachloride, indicating the presence of *iso*butene. After about 1 hr. an oil, b. p. about 50° (presumably *tert.*-butyl chloride), began to reflux, and a solid separated. After 5 hr. the solid had mostly redissolved and oil had almost ceased to reflux. On distillation through a lagged 6-in. Vigreux column no arrest in temperature rise was detected at 50° (*tert.*-butyl chloride) or at 80° (*tert.*-butanol–water), steady distillation first occurring at 100°. On being cooled and made alkaline, a clear solution was obtained (indicating the absence of unchanged sulphonamide). Acidification then precipitated toluene-*p*-sulphonamide (7·55 g., 83·5% yield), m. p. and mixed m. p. 137—137·5° after recrystallisation from water.

The trap contained 2 c.c. of material liquid at −78° (*iso*butene melts at −140°). This was treated with sulphuric acid (1 : 1; 20 c.c.) at −78°, and the trap closed and shaken at −10° for 3 hr. About 0·3 c.c. of oil remained. This had a strong odour of *tert.*-butyl chloride, did not decolorise bromine in carbon tetrachloride, and solidified at −78°. The acid layer was separated and slowly added to stirred ice-cold sodium hydroxide (25 g.) in water (50 c.c.).[46] Distillation of the alkaline liquid gave 2 c.c. of material, b. p. 80—83° (the *tert.*-butanol–water azeotrope, b. p. 80°, containing 70% of butanol). Treatment of the distillate with anhydrous potassium carbonate gave *tert.*-butanol (1 g.) (*p*-nitrobenzoyl ester, m. p. and mixed m. p. 115—116·5°; 3 : 5-dinitrobenzoyl ester, m. p. and mixed m. p. 140·5—141·5°).

(2) Experiment (1) was repeated under different conditions. The sulphonamide (22·7 g.; 0·1 mole) and hydrochloric acid (1 : 1; 125 c.c.) were refluxed under a partial condenser with a cooling tube containing ethyl formate (b. p. 54°). Uncondensed material was passed successively through two traps at 0° and −78°. Steady distillation at 47° lasted for 20 min. After 50 min. the colourless liquid in the first trap was removed (7·8 g.), dried ($CaSO_4$), and distilled; b. p. 50—51°. Some dissolved *iso*butene escaped during the distillation. The liquid, b. p. 50—51°, was characterised as *tert.*-butyl chloride (yield 84·5%) by formation of its Grignard compound and reaction with α-naphthyl *iso*cyanate giving *N*-trimethylacetyl-1-naphthylamine, m. p. and mixed m. p. 147·5°. The second trap (−78°) contained 0·2 c.c. of liquid, presumably *iso*butene. With sulphuric acid and alkali as in (1) an odour of *tert.*-butanol was produced. From the original acid reaction mixture toluene-*p*-sulphonamide (17·1 g.) was obtained in quantitative yield; m. p. and mixed m. p. 136·5—137·5°. The acid had a faint odour of *tert.*-butanol but none was obtained on distillation before or after neutralisation.

N-Benzyltoluene-*p*-sulphonamide (0·1 g.; m. p. 114—115°; Chattaway[47] gives m. p. 115°) was unchanged when refluxed with diluted hydrochloric acid (1 : 1; 4 c.c.) for 5 hr.

N-1-*Phenylethyltoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonyl chloride (19·1 g.; 0·1 mole) in pyridine (30 c.c.) was slowly added to a cooled, stirred solution of 1-phenylethylamine (12·1 g.; 0·1 mole) in pyridine (20 c.c.), kept for 1 hr. at 100°, and poured into water. Recrystallisation of the product from 50% alcohol (charcoal) gave white needles (14·9 g., 54%), m. p. 81—82° (Found : C, 65·3; H, 5·9; N, 5·1; S, 11·5. $C_{15}H_{17}O_2NS$ requires C, 65·4; H, 6·2; N, 5·1; S, 11·6%). The *sulphonamide* is only sparingly soluble in cold, but readily soluble in hot 2N-sodium hydroxide solution, from which it separates unchanged on cooling.

Hydrolysis with hydrochloric acid. The sulphonamide (6·9 g.) and aqueous hydrochloric acid (1 : 1; 80 c.c.) were slowly distilled in nitrogen through an 18-in. vertical air condenser into a tap-funnel containing light petroleum (b. p. 40—60°; 40 c.c.) and a few crystals of quinol. The aqueous layer of the distillate was periodically returned to the reaction flask. After 4 hr. the

[46] Read, *J. Amer. Chem. Soc.*, 1924, **46**, 1514.
[47] Chattaway, *J.*, 1905, **87**, 159.

clear aqueous mixture was cooled (deposit), made alkaline, and washed with ether to remove traces of resin. The alkaline solution on acidification gave toluene-*p*-sulphonamide, m. p. 136—137° (3·52 g., 82%) and mixed m. p. 136·5—137·5°. The light petroleum in the distillate was washed with alkali and with water and dried, yielding an oil (2·1 g.), b. p. 50—67°/12 mm. Redistillation gave two fractions: (*A*) b. p. 35—45°/12 mm. (0·6 g.), and (*B*) b. p. 66—67°/12 mm. (1·17 g.). Fraction (*A*) in carbon tetrachloride with bromine gave styrene dibromide which, when recrystallised from alcohol–water (4 : 1), had m. p. and mixed m. p. 73·5—74°. Fraction (*B*) had an odour of an aralkyl halide. Authentic 1-phenylethyl chloride,[48] purified by Ward's method,[49] had b. p. 67—68°/13 mm. and a similar odour. Fraction *B* was converted into *S*-1-phenylethylthiuronium picrate, m. p. and mixed m. p. 168—169° with an authentic sample of the same m. p. Levy and Campbell[50] give m. p. 167° (Found: C, 43·6; H, 3·6; N, 16·8. Calc. for $C_{15}H_{15}O_7N_5S$: C, 44·0; H, 3·7; N, 17·1%).

Hydrolysis with 90% phosphoric acid. *N*-1-Phenylethyltoluene-*p*-sulphonamide (5·5 g.) and phosphoric acid (*d* 1·75; 10 c.c.) were slowly distilled at 14 mm. from a bath at 100°. The distillate (1·6 g.) collected at −80° was water with one drop of an oil having an odour of styrene. The residue was diluted with water and extracted with ether, from which sodium hydroxide removed toluene-*p*-sulphonamide, m. p. 136·5—137° (2·8 g., 87%). The ether then yielded an oil which gave two fractions on distillation: (*A*) a mobile liquid (1·0 g.) and (*B*) a very viscous oil (0·45 g.). After two fractionations (*A*) had b. p. 155—157°/13 mm., 114—115°/0·4 mm., n_D^{20} 1·5880, and (*B*) boiled at 168—185°/0·15 mm. Analysis showed them to be polymers of styrene. Molecular weight (Rast) determinations were not reproducible, but a semimicro-ebullioscopic determination in benzene showed fraction (*A*) to be dimeric [Found for (*A*): C, 92·3; H, 7·6%; *M*, 214, 213. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%; *M*, 208. Found for (*B*): C, 92·3; H, 7·7%].

Attempted addition of bromine to fraction (*A*) under Stobbe and Posnjak's conditions[51] gave a viscous oil. Stoermer and Kootz[52] showed that distyrenes, containing only a small proportion of 1 : 3-diphenylbut-1-ene, give oils on bromination. Fraction (*A*) contained 30% of diphenylbutene (determined by the modified Wijs method[53]). The infrared spectrum of fraction (*A*) was compared with that of a distyrene (*C*), obtained from styrene and sulphuric acid and containing 10% of 1 : 3-diphenylbut-1-ene.[15] The spectra differed only in the lower intensity of a band at 964 cm.$^{-1}$ in the case of material (*C*). This would be expected if the specimens differed in their content of a diphenylbutene having a *trans*-CH:CH group.

Styrene and phosphoric acid. Freshly-distilled styrene (20 g.) and phosphoric acid (*d* 1·75; 100 c.c.) were heated on the steam-bath for 30 min., with vigorous stirring. The resulting oil (19 g.), extracted by ether, contained no unchanged styrene; on distillation it yielded a dimer (13·5 g.), b. p. 147—152°/0·6 mm., 125—132°/0·1 mm., n_D^{20} 1·5865 (Found: C, 92·4; H, 7·8%; *M*, 195, 199. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%; *M*, 208), which contained 38% of diphenylbutene (determined by the modified Wijs method). A trimer (2·4 g.), b. p. 190—207°/0·15 mm., n_D^{20} 1·5946, was also obtained (Found: C, 92·3; H, 7·8%; *M*, 299, 308. Calc. for $C_{24}H_{24}$: C, 92·3; H, 7·7%; *M*, 312).

Oxidation of N-tert.-*Butyltoluene*-p-*sulphonamide to* N-tert.-*Butyl*-p-*sulphamylbenzoic Acid.*—The sulphonamide (6 g.) was refluxed with potassium permanganate (16 g.) and anhydrous sodium carbonate (9 g.) in water (300 c.c.) for 1 hr. The cooled mixture was then treated with excess of sulphur dioxide, and the resulting white solid separated. It dissolved completely in cold 2N-sodium hydrogen carbonate (50 c.c.). On passing excess of carbon dioxide through the solution there was no precipitate, but on acidification to Congo-red material was precipitated having m. p. 182—183°, unchanged after two recrystallisation from water–ethanol (10 : 1). The *acid* (yield 5·5 g., 68%) formed long needles (Found: C, 51·7; H, 6·0; N, 5·4; S, 12·6. $C_{11}H_{15}O_4NS$ requires C, 51·3; H, 5·9; N, 5·4; S, 12·5%). The *methyl ester* was obtained by use of ethereal diazomethane and had m. p. 124—124·5° (constant) after crystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 53·2; H, 6·1; N, 5·1; S, 11·6. $C_{12}H_{17}O_4NS$ requires C, 53·1; H, 6·3; N, 5·2; S, 11·8%). The ester (1 g.) was refluxed with aqueous hydrochloric acid (1 : 1; 20 c.c.) for 10 min.; an odour of *tert.*-butyl chloride was noticed. A solid which formed was completely soluble in aqueous sodium hydrogen carbonate,

[48] McKenzie and Clough, *J.*, 1913, **103**, 678.
[49] Ward, *J.*, 1927, 445.
[50] Levy and Campbell, *J.*, 1939, 1442.
[51] Stobbe and Posnjak, *Annalen*, 1909, **371**, 287.
[52] Stoermer and Kootz, *Ber.*, 1928, **61**, 2330.
[53] Wild, "Estimation of Organic Compounds," Univ. Press, Cambridge, 1953; Williams and Thomas, *J.*, 1948, 1867.

and after precipitation with hydrochloric acid it had m. p. and mixed m. p. 292—293° with *p*-sulphamylbenzoic acid.

Hydrolysis of N-tert.-*butyl*-p-*sulphamylbenzoic acid.* The acid (12·85 g., 0·05 mole) was heated for 1 hr. with aqueous hydrochloric acid (1 : 1; 120 c.c.) under a partial condenser at 54°. *tert.*-Butyl chloride, b. p. 50—52°, distilled and was characterised by conversion into *N*-trimethylacetyl-1-naphthylamine which when crystallised from ether–light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 147—148°. During the hydrolysis *p*-sulphamylbenzoic acid (9·9 g., 93·5%) separated which, when crystallised from ethanol, melted at 293—294°, not depressing the m. p. (292—293°) of authentic material. The acid (1 g.) was treated in ether (15 c.c.) with a twofold excess of ethereal diazomethane. The ester (0·87 g.; 87·5%) when recrystallised from water–ethanol (5 : 1) had m. p. 180—181·5; the m. p. of a mixture with authentic ester was 180·5—182°.

p-*Sulphamylbenzoic acid.* This was prepared by oxidation of toluene-*p*-sulphonamide with potassium permanganate and was recrystallised from water.[9] It sintered slightly from 275° and melted at 292—293°. The m. p. was the same when the apparatus was slowly heated from room temperature or when the m. p. tube was inserted at 250°. Ash *et al.*[9] give m. p. 283° (decomp.). Other workers record m. p.s ranging from 280° to 286° (Found: C, 41·8; H, 3·8; N, 6·7; S, 15·7. Calc. for $C_7H_7O_4NS$: C, 41·8; H, 3·5; N, 7·0; S, 15·9%).

The acid [2 g. in ether (25 c.c.) or in benzene] reacted only sluggishly with ethereal diazomethane and methanol (1 c.c.) during 24 hr. Extraction of unchanged acid (0·41 g.) with aqueous sodium hydrogen carbonate gave the *ester* (1·3 g., 61%) which, recrystallised twice from alcohol, had m. p. 180·5—182° (Found: C, 44·6; H, 4·1; N, 6·7; S, 14·9. $C_8H_9O_4NS$ requires C, 44·7; H, 4·2; N, 6·5; S, 14·9%).

Oxidation of N-tert.-*Butyltoluene*-p-*sulphonamide*: *Identification of* 2-*Methyl*-2-*nitropropane and* tert.-*Butylamine.*—The sulphonamide (18·2 g.) was refluxed with excess of 6% aqueous permanganate containing 3% of sodium carbonate for 1 hr. Distillation yielded an alkaline aqueous liquid (see below) and a very volatile solid, m. p. 23°, identified as 2-methyl-2-nitropropane by its m. p. and infrared spectrum, which was identical with that of a specimen prepared by permanganate oxidation of *tert.*-butylamine.[38] *N-tert.*-Butyl-*p*-sulphamylbenzoic acid (15·7 g.) was obtained as before.

The spectrum of 2-methyl-2-nitropropane had maxima ($cm.^{-1}$) at: 2967 (s), 2924 (m, sh), 2874 (w, sh), 1548 (vs, sh), 1538 (vs), 1479 (s), 1458 (s), 1408 (s), 1376 (vs), 1348 (vs), 1256—1247 (m, broad), 1186 (m), 1017 (w), 858 (s), 801 (w), (intensities: vs, very strong; s, strong; m, medium; w, weak; sh, shoulder). The strong bands at about 1545 and 1348 $cm.^{-1}$ may be ascribed to the nitro-group, and the bands at 1408, 1376, *ca.* 1250, and 1186 $cm.^{-1}$ to the *tert.*-butyl group.[54]

In another experiment the sulphonamide (8 g.) was refluxed with potassium permanganate (11·13 g.) and anhydrous sodium carbonate (5·5 g.) in water (186 c.c.) (the calculated quantities for oxidation of a methyl to a carboxyl group) for 1·5 hr., the colour of the permanganate then being discharged. 20 C.c. of the mixture were distilled into dilute hydrochloric acid, which was then evaporated, thus removing 2-methyl-2-nitropropane. The residue was identified as *tert.*-butylamine hydrochloride by conversion into the picrate (m. p. and mixed m. p. 198—200°) and into *N-tert.*-butyltoluene-*p*-sulphonamide, m. p. and mixed m. p. 113—114°. The original alkaline mixture was filtered. Extraction of the manganese dioxide yielded unchanged sulphonamide (1·2 g., m. p. 113—114°), and acidification of the filtrate gave *N-tert.*-butyl-*p*-sulphamylbenzoic acid, m. p. 181·5—182°; yield, calc. on the sulphonamide which had reacted, 91%. Concentration of the acid filtrate, which contained sulphate, gave no sodium hydrogen *p*-sulphobenzoate. As this readily separates from acidified salt solutions[55] it was presumably absent.

Oxidation of N-tert.-*butyl*-p-*sulphamylbenzoic acid.* The acid (7 g.) was refluxed with potassium permanganate (21 g.) and anhydrous sodium carbonate (10·5 g.) in water (350 c.c.) until the permanganate was decolorised (9 hr.). A white solid formed in the condenser; this was treated with water, leaving some insoluble 2-methyl-2-nitropropane. Evaporation of the aqueous extract gave a solid which was insoluble in ether and sublimed above 120° without melting (sealed capillary tube). With dilute hydrochloric acid it gave carbon dioxide and *tert.*-butylamine hydrochloride (picrate, m. p. and mixed m. p. 198—200°). The solid was therefore the corresponding carbonate or carbamate. Passage of carbon dioxide into *tert.*-butylamine in moist ether gave a product with the same properties. 2-Methyl-2-nitropropane

[54] Ref. 39, pp. 13, 250.
[55] Smiles and Harrison, *J.*, 1922, **121**, 2022.

and *tert.*-butylamine were again obtained from the mixture. The nitro-compound had m. p. 23°, n_D^{28} 1·3980. Kornblum and Clutter [56] give m. p. 25—26°, n_D^{28} 1·3980. A specimen prepared by their method, dried [$Mg(ClO_4)_2$], and sublimed, had m. p. 23—25°, n_D^{28} 1·3980. Unchanged *N-tert.*-butylsulphamylbenzoic acid (2·8 g.) was removed as before. From the filtrate, faintly acid to Congo-red, sodium hydrogen oxalate separated, identified by the usual reactions and by conversion into its *S*-benzyl*iso*thiuronium salt, m. p. and mixed m. p. 195—196° (decomp.). The concentrated mother-liquors contained sulphate, but no sodium hydrogen *p*-sulphobenzoate could be detected.

Oxidation of p-*sulphamylbenzoic acid.* The acid (5·47 g.; equivalent to 7·0 g. of the *N-tert.*-butylsulphamylbenzoic acid) was oxidised with the same quantity of reagents as in the previous experiment. Decolorisation was complete (14 hr.) and 2·36 g. of unchanged acid were recovered. Concentration of the mixture and treatment as above gave approximately 1 g. of sodium hydrogen oxalate, identified as before [*S*-benzyl*iso*thiuronium salt, m. p. 195—196° (decomp.)].

N-iso*Propyltoluene*-p-*sulphonamide.* This was prepared from *iso*propylamine (17 c.c., 0·2 mole) and toluene-*p*-sulphonyl chloride (38·1 g., 0·2 mole) in pyridine as described for the *N-tert.*-butyl compound. It was purified by solution in warm aqueous sodium hydroxide, precipitation with hydrochloric acid, and crystallisation from aqueous alcohol (charcoal). The *amide* (28·5 g.; 67·5%) had m. p. 49·5—51°. The m. p. does not appear in the literature but is quoted as 51° [56] (Found: C, 56·3; H, 6·8; N, 6·6; S, 14·9. $C_{10}H_{15}O_2NS$ requires C, 56·3; H, 7·1; N, 6·6; S, 15·0%). When it was boiled for 14 hr. with aqueous hydrochloric acid (1 : 1; 230 c.c.) no volatile organic compound distilled and 90% of the sulphonamide was recovered unchanged. The aqueous layer when made alkaline gave a slight ammoniacal odour, presumably due to *iso*propylamine since aspiration through Nessler's solution gave a white precipitate but no brown colour.

Oxidation of N-iso*propyltoluene*-p-*sulphonamide.* A mixture of the sulphonamide (6 g.), potassium permanganate (30 g., 20 equiv. of O per mole), and anhydrous sodium carbonate (15 g.) in water (500 c.c.) was distilled in steam for 1 hr. The acetone in the distillate yielded 0·2 g. of 2 : 4-dinitrophenylhydrazone which, recrystallised from methanol, had m. p. and mixed m. p. 125—125·5°. Treatment of the main reaction mixture with sulphur dioxide and hydrochloric acid yielded *p*-sulphamylbenzoic acid (3·9 g., 68%) which, after recrystallisation from weak aqueous ethanol, had m. p. and mixed m. p. 292—293°. The amount of permanganate required for complete oxidation of the *N-iso*propyltoluene-*p*-sulphonamide to *p*-sulphamylbenzoic acid, carbon dioxide, and water is 25 equiv. per mole. When only 10 equiv. were used (reflux) and all permanganate was reduced, about one-third of the sulphonamide was recovered unchanged, and some toluene-*p*-sulphonamide and *p*-sulphamylbenzoic acid were obtained. By using only 2 equiv. of permanganate in presence of magnesium sulphate the yield of acetone 2 : 4-dinitrophenylhydrazone was 25%, original sulphonamide (67%) was recovered after treatment with sodium hydrogen carbonate, and a crude acid, m. p. 216—217°, which appeared to be a mixture of *p*-sulphamylbenzoic acid and its *N-iso*propyl derivative, was obtained.

Preparation and Oxidation of NN-*Dimethyltoluene*-p-*sulphonamide.*—Aqueous dimethylamine (25%; 20 c.c., 0·11 mole), toluene-*p*-sulphonyl chloride (28·5 g.; 0·15 mole), and 2N-sodium hydroxide (200 c.c.) were warmed for ½ hr. and boiled for ½ hr. The insoluble sulphonamide (18·1 g., 82%) when crystallised from aqueous alcohol (50%) had m. p. 80—81·5°. Chaplin and Hunter [57] give m. p. 80—81° without preparative details. With excess of hot aqueous permanganate–sodium carbonate mixture no aldehyde was evolved. The product (yield, 77·5%), isolated as before, was *p*-sulphamylbenzoic acid, m. p. and mixed m. p. 292—293°. By using 67% of the amount of permanganate required for oxidation to *p*-sulphamylbenzoic acid, carbon dioxide, and water, no toluene-*p*-sulphonamide was obtained; about 10% of the original sulphonamide was recovered and the crude *p*-sulphamylbenzoic acid had m. p. 255—260° and probably contained some of its *NN*-dimethyl derivative.

Oxidation of N-*Methyl- and* N-*Ethyl-toluene*-p-*sulphonamides.*—The sulphonamides were boiled for 1 hr. with excess of alkaline potassium permanganate. In the case of the *N*-methyl compound (5 g.) decolorisation with sulphur dioxide, collection of the precipitate, and concentration of the filtrate yielded a product which, on extraction with aqueous sodium hydrogen carbonate, left 1·2 g. of toluene-*p*-sulphonamide, m. p. and mixed m. p. 136—137°. Acidification and concentration of the extract gave a solid (m. p. 259°; 2·0 g.) which after two

[56] "Organic Reagents for Organic Analysis," Hopkin and Williams, Chadwell Heath, 1950.
[57] Chaplin and Hunter, *J.*, 1937, 1114.

crystallisations from water had m. p. and mixed m. p. 280—281° with authentic *p*-sulphamylbenzoic acid, m. p. 280—281°. The correct m. p. has now been found to be 292—293° (see p. 1761). Similar results were obtained with *N*-ethyltoluene-*p*-sulphonamide.

Oxidation of Toluene-p-sulphonanilide.—The sulphonanilide (4·94 g., 0·02 mole) was refluxed with potassium permanganate (42 g.) and magnesium sulphate (42 g.) in water (700 c.c.) for 1 hr. The mixture was treated as before, and yielded *p*-sulphamylbenzoic acid (3·4 g., 84·5%), m. p. and mixed m. p. 292—293° (Found: C, 41·7; H, 3·6. Calc. for $C_7H_7O_4NS$: C, 41·8; H, 3·5%); methyl ester, m. p. and mixed m. p. 181—182°. The same product was obtained in good yield when sodium carbonate replaced magnesium sulphate in the oxidation mixture.

Comparison of the Oxidation of Acetanilide and Toluene-p-sulphonanilide with Potassium Permanganate.—Acetanilide (2·7 g., 0·02 mole), potassium permanganate (8 g.), magnesium sulphate heptahydrate (8 g.), and water (270 c.c.) were boiled for ½ hr. Excess of permanganate was still present. Treatment with sulphur dioxide, filtration, and addition of ammonium sulphate to the filtrate yielded unchanged acetanilide (1·3 g.; recovery 48%). Toluene-*p*-sulphonanilide (4·94 g., 0·02 mole) was oxidised with the same quantities of materials. No permanganate remained after 3 minutes' boiling. After sulphur dioxide treatment and acidification, the resulting solid (3·6 g.) on extraction with aqueous sodium hydrogen carbonate was shown by m. p. and mixed m. p. (99—101°) to be the unchanged anilide (recovery 72%). Acidification of the extract gave only a trace of material, m. p. >250°. Concentration of the original filtrate yielded toluene-*p*-sulphonamide (0·1 g.; m. p. and mixed m. p. 137—137·5°). These results clearly show that toluene-*p*-sulphonanilide is much more susceptible to destructive oxidation than is acetanilide.

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346. *The Preparation and Stability of Dialkyl Chloroboronates.*

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The preparation of a number of dialkyl chloroboronates, $BCl(OR)_2$, by reaction of either boron trichloride or alkyl dichloroboronites, $BCl_2{\cdot}OR$, with either alcohols or trialkyl borates has been investigated. The chloroboronates may further undergo either an alkyl chloride-producing reaction, accompanied by an olefin-producing elimination reaction, or a disproportionation reaction, depending upon the experimental conditions. The stability of dialkyl chloroboronates with respect to the former reaction depends on both electronic and steric factors. A probable mechanism for this reaction is offered, based on (1) the relative stability of chloroboronates when R is varied, (2) stereochemical features (optical activity and molecular rearrangements), and (3) the influence of catalysts. Results are compared with those obtained with alkyl dichloroboronites in a previous investigation.[1]

In two earlier papers[2,3] experiments on alcohol–boron trichloride–borate systems were described, in which dialkyl chloroboronates, $BCl(OR)_2$, containing primary (Bu^n and Bu^i), but not secondary or tertiary alkyl groups, were isolated. The present paper reports methods of preparation of chloroboronates, the stoicheiometry of their decomposition, and constitutional, stereochemical, and environmental factors influencing such decomposition reactions. Experiments are described concerning the systems involving *n*-propyl, the four isomeric butyl, *neo*pentyl, 1 : 2 : 2-trimethylpropyl, 1-octyl, and 1-methylheptyl radicals. The results are available for comparison with corresponding experiments[1] with alkyl dichloroboronites, $BCl_2{\cdot}OR$.

[1] Gerrard and Lappert, *J.*, 1955, 3084.
[2] *Idem*, *J.*, 1951, 1020.
[3] *Idem*, *J.*, 1951, 2545.

Interaction between (*a*) boron trichloride or alkyl dichloroboronites and (*b*) alcohols or trialkyl borates, in the proportions indicated by (1)—(4), gave quantitative yields of the chloroboronates. In view of the difficulty in handling boron trichloride, methods (2) and (4) are preferred, but are only suitable for chloroboronates having primary alkyl groups, as the corresponding alkyl dichloroboronites, required as starting materials, are sufficiently stable only in those cases.[1]

$$(1)\quad BCl_3 + 2ROH \longrightarrow BCl(OR)_2 + 2HCl$$
$$(2)\quad BCl_2{\cdot}OR + ROH \longrightarrow BCl(OR)_2 + HCl$$
$$(3)\quad BCl_3 + 2B(OR)_3 \longrightarrow 3BCl(OR)_2$$
$$(4)\quad BCl_2{\cdot}OR + B(OR)_3 \longrightarrow 2BCl(OR)_2$$

The chloroboronates could react further in one of three ways—an alkyl chloride-producing decomposition (5), accompanied to a relatively small extent by an olefin-producing elimination reaction (6), and a disproportionation (7).

$$(5)\quad 3BCl(OR)_2 \longrightarrow B_2O_3 + B(OR)_3 + 3RCl$$
$$(6)\quad 3BCl(OR)_2 \longrightarrow B_2O_3 + B(OR)_3 + 3HCl + 3\ Olefin$$
$$(7)\quad 2BCl(OR)_2 \rightleftharpoons B(OR)_3 + BCl_2{\cdot}OR$$
$$2BCl_2{\cdot}OR \rightleftharpoons BCl_3 + BCl(OR)_2$$

According to experimental conditions either (7), or (5) and (6) together, were observed. At pressures equal to or greater than atmospheric and under reflux or sealed-tube conditions, decomposition (5) with (6) was observed. Under reflux, by reduction of pressure, slow disproportionation (7) was observed. Of these three reactions, (7) was reversible and so was (5), but in this case only when the group R was primary and straight-chained. The reversibility of the alkyl (primary) chloride-producing decomposition illustrates a difference from the dichloroboronites. A further difference is the far greater facility shown by the latter to disproportionate.

Distillation of the chloroboronates at atmospheric pressure was not possible in view of reactions (5)—(7), but at low pressures, such that the b. p. was below 45°, the *n*-propyl, *n*- and *iso*-butyl, *neo*pentyl, and 1 : 2 : 2-trimethylpropyl chloroboronates could be distilled without significant decomposition (<3%). The *sec.*-butyl and the 1-methylheptyl ester, however, decomposed [(5) and (6)], and the 1-octyl ester disproportionated (7) presumably because of the higher temperature that had to be used. In view of this difficulty, the experiments on the chloroboronates were carried out on undistilled samples, from which volatile materials (boron trichloride, hydrogen chloride, alkyl chlorides, or alkyl dichloroboronites) were removed by application of a suitable vacuum. The resultant samples were analytically very pure, and further, the molecular refractivities calculated from the measured refractive indices and densities were in good agreement (see Table 1) with the

TABLE 1.*

R in $BCl(OR)_2$	Pr^n	Bu^n	Bu^i	Bu^s	$CMe_2{\cdot}CH_2$	$CHMeBu^t$	C_8H_{17}	$CHMe{\cdot}C_6H_{13}$
Found : $[R_L]_D$...	41·8	51·0	50·6	50·7	60·2	69·3	88·2	87·3
Calc. : $[R_L]_D$ ...	41·8	51·0	51·0	51·0	60·3	69·5	88·0	88·0

* The author is grateful to a referee for suggesting the advisability of computing these figures.

values calculated from Eisenlohr's data on carbon, hydrogen, oxygen, and chlorine atomic refractivities,[4] and an average value for boron of 2·65, calculated from Cowley and Partington's [5] and Arbuzov and Vinogradova's data [6] on trialkyl borates.

Either reaction (5) or (7) has previously been regarded as characteristic of a particular branching. Thus Bu^n and Bu^i were thought to afford reaction (5) only,[3] whilst for di-2-chloroethyl [7] and for diphenyl [8] chloroboronate the characteristic reaction was (7).

[4] Eisenlohr, *Z. phys. Chem.*, 1910, **75**, 585.
[5] Cowley and Partington, *Nature*, 1935, **136**, 643.
[6] Arbuzov and Vinogradova, *Compt. rend. Acad. Sci. U.R.S.S.*, 1947, **55**, 411.
[7] Edwards, Gerrard, and Lappert, *J.*, 1955, 1470.
[8] Colclough, Gerrard, and Lappert, *ibid.*, p. 907.

Factors governing reaction (5) were studied under three headings.

(a) *Influence of Constitutional Factors.*—The stability of chloroboronates varied widely with change in the alkyl group, R. The *tert.*-butyl ester was unstable at 20° (88% decomposition in 20 min.). Of the esters having secondary alkyl groupings the stability increased with length of chain and extent of branching in the alkyl groups. Thus the *sec.*-butyl ester was less stable than the 1-methylheptyl ester and di-1 : 2 : 2-trimethylpropyl chloroboronate was completely unchanged after 6 days at 20° and indeed was more stable at 150° than short-chain primary esters such as the di-*n*-propyl and di-*n*-butyl chloroboronates. The primary dialkyl chloroboronates were stable at 20°, but at 150° the stability increased with length of chain and with extent of branching. Thus the 1-octyl and *neo*pentyl esters were unchanged after 5 hr. at 150°, whereas the *n*-propyl and *n*- and *iso*-butyl ester were almost completely decomposed. The *iso*- was more stable than the *n*-butyl ester which in turn was more stable than the *n*-propyl. Similar results were observed at 100°. The results are summarised in Table 9.

It is clear that the stability of dialkyl chloroboronates is dependent both on the degree of electron release at the alcoholic carbon atom and also on steric factors, in contrast to the stability ranges found for alkyl dichloroboronites, where the electronic factor was the controlling, if not the only, criterion of stability.[1]

(b) *Influence of Stereochemical Factors.*—Wagner–Meerwein type rearrangement has previously been demonstrated in the decomposition of di*iso*butyl chloroboronate to *tert.*-butyl chloride.[3] Two other examples are now given:

$$Me_2C{\cdot}CH_2{-} \longrightarrow Me_2EtC{-} \text{ and } Me_2C{\cdot}CHMe{-} \longrightarrow PrMe_2C{-}$$

Whereas decomposition of (+)-1-methylheptyl dichloroboronite afforded much racemised 2-chloro-octane,[1] the decomposition of the corresponding chloroboronate is now shown to give (−)-2-chloro-octane with very little loss of activity.

(c) *Influence of Environmental Factors.*—The isomeric dibutyl chloroboronates are considerably more stable than has hitherto been believed. The lower stability reported earlier[3] is due to very small traces (<0·1%) of Lewis acid impurity then present, which catalysed decomposition. The influence of such catalysts on the decomposition of chloroboronates is general. Of the compounds tried, hydrogen chloride, alkyl chlorides, trialkyl borates, and *n*-pentane had no effect on the decompositions; Lewis acids such as ferric and aluminium chloride were very effective, as also to a smaller extent were alkyl dichloroboronites. For example, the addition of ferric chloride (0·05%) to di-*n*-butyl chloroboronate at 20° caused instant decomposition. Similar results were observed with the other esters; the results are summarised in Table 10. By contrast, diethyl ether, a Lewis base, had a stabilising effect.

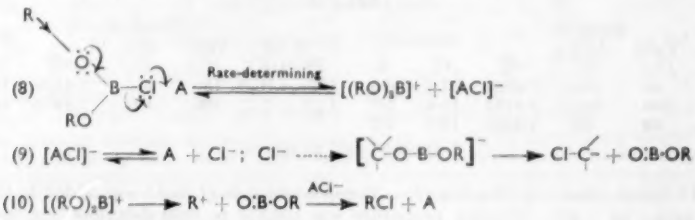
With the *iso*butyl, *neo*pentyl, and (+)-1-methylheptyl esters, such catalytic decomposition did not affect the steric course of the reactions.

The acceleration of decomposition produced by ferric and aluminium chloride is comparable to that observed with dichloroboronites.[1]

The Mechanism of Decomposition.—The mechanism of decomposition (5) of dialkyl chloroboronates is considered to involve a rate-determining initial fission of the B–Cl bond, depending on two factors, the degree of electron release (+*I*) from the alkyl group, and the action of a second molecule of the ester, designated "A" in (8), which functions as an electrophilic catalyst and thus facilitates heterolysis of the B–Cl bond. Other Lewis acids, such as those mentioned in (c) (above) may also function as "A" in this way. The efficiency of "A" is dependent on two factors, its strength as an electrophile and the steric availability of the electron-deficient atom. If this atom is shielded, as in the uncatalysed decomposition of highly branched dialkyl chloroboronates, the power of "A" as an electrophile is low or negligible. This duality of mechanistic factors explains the observed influence of constitutional and environmental variations. The greater emphasis on steric factors in the decomposition of chloroboronates than in that of dichloroboronites is also clear.

Subsequent steps in the decomposition mechanism appear to depend on the nature of the alkyl group. Those groups which are normally not hindered with respect to S_N2

" in-line " attack choose this mode of reaction (9), whilst those hindered with respect to such attack react by an S_N1 carbonium-ion mechanism (10). These suggestions are put forward to account for the observed stereochemical influences.



The metaborates, BO·OR, suggested as intermediates, are finally considered to decompose :

$$(11)\ 3BO{\cdot}OR \longrightarrow B(OR)_3 + B_3O_3$$

The probability of preponderance of either the S_N2 (9) or the S_N1 mechanism (10) for a particular group R, will depend on the relative rates of these reactions. The stability of $[(RO)_2B]^+$ is evidently sufficient to permit (9) to take place if the group R is such that it is normally responsive to S_N2 replacements. This is a contrasting result to that found [1] with dichloroboronites, where even with such groups, an S_N1 result was obtained. This is doubtless due to the lower stability of $[BCl{\cdot}OR]^+$ than of $[(RO)_2B]^+$; the greater stability of the latter may be due to its symmetry.

Experimental

General Procedure.—Reagents were prepared or purified by the methods outlined earlier.[1] Compounds containing boron, or boron as well as chlorine atoms attached to a boron atom, were analysed by cold-water hydrolysis in an enclosed system and titration with carbonate-free sodium hydroxide to successively a methyl-orange (Cl) and a phenolphthalein (B) end-point, the latter titration being carried out in the presence of mannitol. Compounds containing a chlorine atom attached to a carbon atom were analysed for chlorine by the Volhard method, after previous hydrolysis with boiling ethanolic potassium hydroxide.

Dialkyl Chloroboronates by Reaction (1).—The alcohol (2 mols.) was added dropwise to boron trichloride (1 mol.) at −80°. The outlet to the reaction vessel was connected to potassium hydroxide absorption tubes in order to collect the liberated hydrogen chloride. At the end of the addition, the mixture was allowed to warm to 20° and was then kept at 20°/15—20 mm. for 30 min., whilst being mechanically shaken. The residual oil was the chloroboronate. The results are shown in Table 2 (for Bu^n and Bu^i, see ref. 3; for Me and Et, see ref. 9; for 2-chloroethyl, see ref. 7); all the *esters* are new compounds. Reagents were used in 0·01—0·05-molar amounts and the reverse order of addition gave substantially similar results.

Table 2.

R in $BCl(OR)_2$	Yield (%)	Yield of HCl (%)	Properties of $BCl(OR)_2$ n_D^{20}	d_4^{20}	Found (%): Cl	Found (%): B	Required (%): Cl	Required (%): B
Pr^n	98	100	1·4028	0·959	21·4	6·6	21·6	6·6
Bu^s	98	99	1·4017	0·924	18·4	5·8	18·4	5·6
$CMe_2{\cdot}CH_2$ *	100	100	1·4102	0·906	16·1	5·1	16·1	4·9
$CHMeBu^t$	100	98	1·4165	0·901	14·2	4·4	14·3	4·4
C_8H_{17}	99	98	1·4380	0·906	11·6	3·7	11·7	3·6
$CHMe{\cdot}C_6H_{13}$ †	100	97	1·4277	0·897	11·6	3·7	11·7	3·6

* Pentane used as solvent, as alcohol is a solid.
† α_D^{20} +20·0° from ROH having α_D^{20} +7·72°.

Dialkyl Chloroboronates by Reaction (2).—The alcohol (1 mol.) was added to the dichloroboronite [1] (1 mol.) at −80°. Further procedure was similar to that described for reaction (1).

[9] Wiberg and Sütterlin, *Z. anorg. Chem.*, 1931, **202**, 31.

Results are shown in Table 3. The method was not satisfactory for the esters having secondary alkyl groups, as the corresponding dichloroboronites are unstable.[1]

TABLE 3.

R in $BCl(OR)_2$	Yield (%)	Yield of HCl (%)	n_D^{20}	Found (%): Cl	Found (%): B	R in $BCl(OR)_2$	Yield (%)	Yield of HCl (%)	n_D^{20}	Found (%): Cl	Found (%): B
Pr^n	98	100	1·4024	21·5	6·6	$CMe_2{\cdot}CH_2$ *	100	100	1·4100	16·1	5·0
Bu^n	100	100	1·4132	18·4	5·7	C_8H_{17}	100	100	1·4378	11·6	3·7
Bu^i	98	99	1·4055	18·3	5·7						

* Pentane used as solvent.

Dialkyl Chloroboronates by Reaction (3).—Boron trichloride (1 mol.) was added to the trialkyl borate (2 mols.) at −80°. Further procedure was similar to that described for reaction (1), except that instead of potassium hydroxide absorption tubes, a silica-gel drying tube was attached to the apparatus. Results are shown in Table 4 (for Bu^n and Bu^i, see ref. 3; for Me and Et, see ref. 10; for 2-chloroethyl, see ref. 7).

TABLE 4.

R in $BCl(OR)_2$	Yield (%)	n_D^{20}	Found (%): Cl	Found (%): B	R in $BCl(OR)_2$	Yield (%)	n_D^{20}	Found (%): Cl	Found (%): B
Pr^n	97	1·4027	21·3	6·6	$CHMeBu^t$ ...	100	1·4169	14·2	4·5
Bu^s	98	1·4013	18·3	5·7	C_8H_{17}	100	1·4379	11·4	3·6
$CMe_2{\cdot}CH_2$ ...	100	1·4106	16·1	4·9	$CHMe{\cdot}C_6H_{13}$ *	99	1·4283	11·6	3·7

* α_D^{20} +20·4° from $B(OR)_3$ having α_D^{20} +28·7°.

Dialkyl Chloroboronates by Reaction (4).—The dichloroboronite (1 mol.) was added to the trialkyl borate (1 mol.) at −80° and subsequent procedure was as described for reaction (3). Results are shown in Table 5. The method was not tried for chloroboronates having secondary alkyl groupings.

TABLE 5.

R in $BCl(OR)_2$	Yield (%)	n_D^{20}	Found (%): Cl	Found (%): B	R in $BCl(OR)_2$	Yield (%)	n_D^{20}	Found (%): Cl	Found (%): B
Pr^n	97	1·4020	21·5	6·6	$CMe_2{\cdot}CH_2$ ...	100	1·4106	16·0	5·0
Bu^n	99	1·4134	18·3	5·7	C_8H_{17}	100	1·4384	11·6	3·6
Bu^i	100	1·4055	18·4	5·6					

Decomposition (5) *and* (6) *of Dialkyl Chloroboronates.*—The purpose of these experiments was to establish the stoicheiometry of the decompositions. Conditions (*e.g.*, absence or presence of various catalysts) are not stated (except that in none was reduced pressure used) because, as a result of many experiments, it was seen that these did not affect the stoicheiometry of the reactions or the nature of the halide (optical activity and molecular rearrangement results) obtained. The present results are additional to those on the four isomeric butyl esters.[3] Yields are recorded in Table 6, and the results for the characterisation of the alkyl halides and trialkyl borates are shown in Table 7.

TABLE 6.

R in $BCl(OR)_2$		Pr^n	$CMe_2{\cdot}CH_2$	$CHMeBu^t$	C_8H_{17}	$CHMe{\cdot}C_6H_{13}$
Yield (%) of	B_2O_3	95	98	96	100	98
	$B(OR)_3$ ...	93	84	90	98	92
	RCl	79	88	89	97	51 *

* Also octene (35%). The mixture was separated by distillation and by bromination. The dibromide had b. p. 110—111°/13 mm., n_D^{16} 1·4894.

The proportion of olefin formed [reaction (6)] in the decomposition of chloroboronates was small, except for the 1-methylheptyl ester. That it is formed was demonstrated with the *n*-butyl ester. The chloroboronate (11·30 g.) was heated for 4 hr. at 100° under reflux in the presence of a trace of ferric chloride. The outlet of the condenser was connected through a soda-lime trap (to absorb hydrogen chloride) to two Herschel bottles, each containing bromine (4 c.c.) in chloroform (10 c.c.). The bromine solutions were combined and the chloroform and

[10] Wiberg and Smedsrud, *ibid.*, 1935, **225**, 204.

TABLE 7.

R in $BCl(OR)_2$	Characterisation of RCl: B. p. (mm.)	n_D^{20}	Found: Cl (%)	Calc.: Cl (%)	Characterisation of $B(OR)_2$: B. p. (mm.)	n_D^{20}	Found: B (%)	Calc.: B (%)
Pr^n	45—47°	1·3878	—	—	175—177°	1·3969	5·6	5·8
$CMe_2{\cdot}CH_2$ * ...	85	1·4054	32·8	33·2	113(12)	— (m.p. 53—54°)	4·1	4·0
$CHMeBu^t$ * ...	109	1·4180	29·0	29·4	72—74(0·3)	1·4150	3·3	3·2
C_8H_{17}	69—71(15)	1·4302	23·8	23·9	158—160(0·1)	1·4377	3·2	2·7
$CHMe{\cdot}C_6H_{13}$ †	61(14)	1·4275	23·7	23·9	135—137(0·1)	1·4298	2·8	2·7

* The chlorides were also analysed for tertiary alkyl chloride, by hydrolysing weighed samples in dilute nitric acid in the cold (48 hr.) and a subsequent Volhard titration. Earlier work had shown that under these conditions only a tertiary and not a secondary chloride was thus hydrolysed.[1] The results were 85% *neo*pentyl chloride in the *neo*pentyl system and 98% of a *tert.*-hexyl chloride in the 1 : 2 : 2-trimethylpropyl system.

† The chloroboronate was prepared from a (+)-tri-1-methylheptyl borate sample [reaction (3)] having α_D^{20} +14·6°. The borate from decomposition of the chloroboronate had the same activity, whilst the 2-chloro-octane had α_D^{20} −11·8°.

much of the excess of bromine were removed in a vacuum. The small residue was dissolved in ether (10 c.c.), washed ($NaHSO_3$), and dried ($CaCl_2$). The ether was removed by distillation and the residue (0·50 g.) was 1 : 2-dibromobutane, b. p. 164°/760 mm., n_D^{18} 1·5138, equivalent to but-1-ene (0·13 g., 4%).

Disproportionation (7) *of Dialkyl Chloroboronates.*—(a) n-*Butyl.* The ester (4·00 g.) was heated for 28 hr. at 80° under reflux at 1 mm. A residue (2·40 g.), n_D^{20} 1·4101, remained, which was a mixture of tri-*n*-butyl borate (59%) and di-*n*-butyl chloroboronate (41%) (Found: Cl, 7·5; B, 5·1. Calc. for such a mixture: Cl, 7·5; B, 5·1%; n_D^{20} 1·4121). A condensate had collected in a trap cooled to −80°, which after two distillations afforded *n*-butyl dichloroboronite (0·46 g.), b. p. 38—41°/19 mm., n_D^{20} 1·4160 (Found: Cl, 45·3; B, 6·9. Calc. for $C_4H_9OCl_2B$: Cl, 45·8; B, 7·0%).

(b) Very similar results were obtained with the *iso*butyl and the *n*-propyl ester.

Distillation of Chloroboronates.—The chloroboronates shown in Table 8 were distilled. In each case the reduced pressure employed was so chosen that the compounds could be distilled in the range 30—45°. Under these conditions the corresponding dichloroboronites and alkyl chlorides are gaseous, except the 1-octyl ester, which consequently underwent appreciable disproportionation (7). In the cases where distillation was possible, significant disproportionation (about 15%) was noted (*i.e.*, a dichloroboronite condensate and a trialkyl borate residue). The di-*sec.*-butyl and di-1-methylheptyl chloroboronates could not be distilled owing to decomposition [(5) and (6)].

TABLE 8.

R in $BCl(OR)_2$	B. p. (mm.)	n_D^{20}	Found (%): Cl	B	R in $BCl(OR)_2$	B. p. (mm.)	n_D^{20}	Found (%): Cl	B
Pr^n	36°(6)	1·4018	21·3	6·5	$CMe_2{\cdot}CH_2$	30°(0·2)	1·4110	16·0	4·8
Bu^n	40(0·25)	1·4128	18·1	5·5	$CHMeBu^t$	35(0·015)	1·4180	14·2	4·4
Bu^i	32(0·2)	1·4070	18·2	5·6	$[C_8H_{17}$ ...	40—75(0·01)	1·4338	18·3	4·0]

TABLE 9.

R in $BCl(OR)_2$	Time (hr.)	Temp.	Decompn. (%)	R in $BCl(OR)_2$	Time (hr.)	Temp.	Decompn. (%)
Bu^s	1/3	20°	0·5	$CMe_2{\cdot}CH_2$	5	150*	0
Bu^s	2½	20	2	$CHMeBu^t$	1	150	2
Bu^s	22	20	13	"	2	150	35
Bu^s	72	20	37	"	5	150	68
$CHMe{\cdot}C_6H_{13}$	72	20	1	C_8H_{17}	5	150	0
"	42 days	20	26	Bu^n	1	100	5
$CHMeBu^t$ ...	144	20	0	Bu^n	3	100	23
Pr^n *	1	150	90	Bu^n	5	100	38
Pr^n	2	150	95	Bu^i	1	100	0
Bu^n *	1	150	62·5	Bu^i	3	100	1
Bu^n	2	150	88	Bu^i	5	100	1·5
Bu^i	1	150	3	$CMe_2{\cdot}CH_2$	28	200	92
Bu^i	2	150	56				

* Only in these examples was there evidence of reversibility. Thus samples which had been heated for 5 hr. at 150°, when subsequently left for 36 hr. at 20°, contained more chloroboronate (Pr^n, 80%; Bu^n, 60%).

Stability of Dialkyl Chloroboronates.—The only tertiary ester investigated was di-*tert.*-butyl chloroboronate. This was not isolated at 20°, when method (4) was used, the mixture being 88% decomposed after 20 min. For the other esters, the results for non-catalysed decompositions are shown in Table 9, and, for decompositions at 20° in presence of added substances, in Table 10. At 20° all the primary esters (Pr^n, Bu^n, and Bu^i, $CMe_3{\cdot}CH_2$, and C_8H_{17}) were still pure after 3 weeks.

TABLE 10.

R in $BCl(OR)_2$	Time (hr.)	Added substance and amount	Decompn. (%)	R in $BCl(OR)_2$	Time (hr.)	Added substance and amount	Decompn. (%)
Bu^n	1	HCl (saturated)	<2	Bu^n	<5 min.	$AlCl_3$ (2%)	99
Bu^n * ...	1 min.	$FeCl_3$ (0·05%)	98	$CMe_3{\cdot}CH_2$ ...	1	$FeCl_3$ (2%)	96
Bu^n ...	48	$FeCl_3$ (0·05%) + $B(OBu^n)_3$ (1 mol.)	98	Bu^s	2½	BCl_3 † (4%)	45
				$CHMe{\cdot}C_6H_{13}$	2½	BCl_3 † (4%)	25
Bu^n ...	48	$FeCl_3$ (0·05%) + Bu^nCl (1 mol.)	94	Bu^s	23	BCl_3 † (4%)	95
				$CHMe_2{\cdot}C_6H_{13}$	12 days	BCl_3 † (4%)	95
Bu^n ...	48	$FeCl_3$ (0·05%) + $C_5H_{12}{}^n$ (1 mol.)	93	,,	23	BCl_3 † (4%)	55
Bu^n ...	48	$FeCl_3$ (0·05%) + Et_2O (1 mol.)	34				

* Temp. rose from 16° to 68°.

† The addition of BCl_3 to chloroboronates has been considered as equivalent to formation of $BCl_2{\cdot}OR$ in the mixture (see discussion).

The stabilities were estimated by heating weighed samples in sealed tubes and analysing the mixtures after arbitrary time intervals by breaking the tubes under water in stoppered flasks and titrating the liberated hydrogen chloride to a methyl-orange end-point (the chloroboronates on hydrolysis in cold water instantly evolve all the chlorine as HCl; the alkyl halides do not).

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347. *Photochemical Changes of Some Deoxybenzoins.*

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In absence of air, deoxybenzoin undergoes photolysis to dibenzyl, benzaldehyde, didesyl, and an amorphous solid, by a free-radical mechanism. The existence of benzaldehyde is explicable if benzoyl radicals dehydrogenate deoxybenzoin to free desyl radicals. Some deoxybenzoins substituted in the aryl and the methylene group undergo analogous photolyses.

In air and light, deoxybenzoin and its 4 : 4′-disubstituted derivatives are oxidised to aldehydic and acidic products, probably *via* a hydroperoxide. Methylene-substituted deoxybenzoins resist such photolysis.

So far as we are aware, little is known regarding the photolysis of deoxybenzoins (I). Paterno, Chieffi, and Perret[1] and Cohen,[2] however, obtained a deoxybenzoinpinacol,

$$4\text{-}X{\cdot}C_6H_4{\cdot}CO{\cdot}CHR{\cdot}C_6H_4{\cdot}X'\text{-}4' \quad (I)$$

benzoic acid, and a resin when deoxybenzoin was irradiated in presence of toluene or ethanol. In the light of this and of our observation that deoxybenzoin undergoes an obvious change on exposure to air and light, the photolysis of this ketone and ten of its derivatives has been systematically studied.

The deoxybenzoins were chosen with a view to determining the influence of the substituent groups on the susceptibility of the ketones to photochemical changes, the substituents (X, X′) in the phenyl groups being methoxy or nitro, and those (R) on the

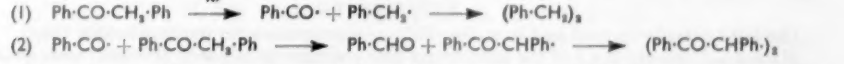
[1] Paternò, Chieffi, and Perret, *Gazzetta*, 1914, **44**, I, 151.
[2] Cohen, *Chem. Weekblad*, 1916, **13**, 902.

methylene group being methyl, ethyl, phenyl, or diphenyl, and, of course, deoxybenzoin itself. These were irradiated in benzene in the absence and in the presence of air, and in certain cases pyridine was added to enhance enolisation.

Photolysis in Absence of Air.—Irradiation of deoxybenzoin in an atmosphere of carbon dioxide under the conditions specified in the Experimental section led to the formation of dibenzyl, didesyl, benzaldehyde, and an amorphous product. However, the isolation of these photolysis products from unchanged deoxybenzoin was difficult and caused formation of traces of benzoic acid.

On the other hand, irradiation of deozybenzoins substituted in an aryl group (4-methoxy-, 4 : 4′-dimethoxy-, 4′-nitro-, 4-methoxy-4′-nitro-deoxybenzoin) did not effect substantial degradation, though traces of *p*-anisaldehyde and a resin were obtained from the first member.

The results support the annexed reaction scheme, in which the benzaldehyde results from the reaction between a benzoyl radical and a deoxybenzoin molecule.



Unlike those substituted in the aryl group, deoxybenzoins substituted in the methylene group undergo profound change. The results so far obtained are in agreement with the mechanism proposed. This may be exemplified by the photolysis of the deoxybenzoin (I; X = X′ = H, R = Me) to benzaldehyde, *meso*- and (±)-2 : 3-diphenylbutane, and an amorphous solid, which requires rupture of the excited molecule to free benzoyl, 1-phenyl-

TABLE 1.

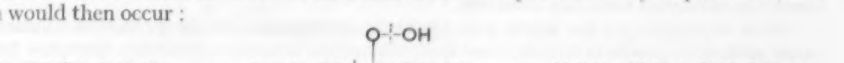
Deoxybenzoin (I)				
X	X′	R	Aldehyde	Dibenzyl
H	H	H	Ph·CHO	Dibenzyl
H	H	Me	,,	*meso*- and (±)-2 : 3-Diphenylbutane
H	H	Et	,,	*meso*-3 : 4-Diphenylhexane
OMe	OMe	Me	*p*-MeO·C$_6$H$_4$·CHO	*meso*- and (±)-2 : 3-Di-(*p*-methoxyphenyl)butane
OMe	OMe	Et	,,	*meso*-Hexœstrol dimethyl ether
H	H	Ph	Ph·CHO	*sym*-Tetraphenylethane

ethyl, α-methyldesyl, and hydrogen radicals. Nevertheless, experimental evidence for the existence of α-methyldesyl radicals is lacking since di-α-methyldesyl could not be separated.

Likewise, three ethyl-substituted deoxybenzoins gave the corresponding aldehydes and dibenzyls (which possess œstrogenic activity). Contrary to Schönberg and Mostafa,[3] the derivative (I; X = X′ = H, R = Ph) is susceptible to irradiation, giving benzaldehyde, *sym*-tetraphenylethane, and an amorphous solid. The diphenyl derivative, however, failed to undergo a change, in agreement with Banchetti's observation.[4]

Photolysis in Presence of Air.—When the above-mentioned deoxybenzoins were irradiated in contact with dry air most of the degradation products obtained by irradiation in the absence of air were isolated, together with acidic and aldehydic degradation products. For example, deoxybenzoin gave benzaldehyde and benzoic acid in appreciable quantities, and peroxides were also detected; dibenzyl and didesyl were not isolated. Similarly, deoxybenzoins substituted in the aryl group gave, in air, the appropriate substituted benzoic acids and benzaldehydes.

There is evidence that ketones are autoxidised in the α-position to hydroperoxides, and fission would then occur :



On the other hand, as has been shown above, photolysis in the absence of air gives rise to the isomeric aldehyde X·C$_6$H$_4$·CHO : if both these reactions occur concurrently then,

[3] Schönberg and Mostafa, *J.*, 1945, 659.
[4] Banchetti, *Gazzetta*, 1941, **71**, 685.

when X = OMe and X′ = H, the products of the combined reactions would be benzoic and *p*-anisic acid, and benzaldehyde and *p*-anisaldehyde, which is what is found.

Photolysis of 2-chlorodeoxybenzoin, involving peroxide formation, was studied by Jenkins [5] who obtained *o*-chlorobenzoic acid and benzaldehyde arising from *o*-chlorobenzoyl and benzyl residues. On the contrary, photolysis of the methylene-substituted deoxybenzoins did not seem to involve autoxidation since peroxides could not be detected and lower aromatic ketones were not isolated. This may be because, in some cases, the mobility of the hydrogen atom attached to tertiary carbon (>CH–), necessary for peroxide formation, is restricted. Nevertheless, the aldehydes and substituted dibenzyls isolated may be attributed to photolysis.

In most of the photolyses, amorphous products were amongst those isolated. Analyses of some of these did not identify them as polydidesyls or polydeoxybenzoins. The identity of the substituted dibenzyls was established by analysis and by comparison with authentic specimens prepared by the hydrogenation of the corresponding ketazines.[6]

Experimental

The light petroleum used had b. p. 60—80°. All reagents were purified before use.

Method.—Portions (2 g.) of the anhydrous deoxybenzoin in benzene (100 ml.) were placed in four series of Pyrex photochemical tubes, of which two were sealed in an atmosphere of carbon dioxide with, and without, pyridine (10 ml. per tube) severally. The other two series, one with, and one without, pyridine were irradiated in contact with dry air. The specimens were exposed to sunlight in Alexandria, Egypt, for 30 days during March—June. A control sample for each of the four series was kept in the dark and no change in them was perceptible.

The peroxides found in some of the aerated samples were detected by the method described by Green and Schoetzow.[7]

Estimation of acidic and aldehydic components. The photolysed deoxybenzoin solutions were diluted with ether or benzene, shaken with saturated sodium hydrogen carbonate solution (3 × 20 ml.), and washed with water (2 × 20 ml.). To the combined sodium hydrogen carbonate extracts and water washings, 2N-hydrochloric acid (150 ml.) was added. The acid mixture was extracted with ether (2 × 100 ml.), and the extract washed with ice-cold water (3 × 20 ml.). The acid residue recovered from the ether was weighed, dissolved in 50% neutral ethanol (*ca.* 50 ml.), and titrated against 0·05N-sodium hydroxide (phenolphthalein), whence the amounts of the acids were determined. In the case of the unsymmetrically substituted deoxybenzoins the percentage weights of the mixed acids were derived by calculation; the component acids were separated by fractional crystallisation, and their identities were confirmed by mixed m. p. determinations.

When pyridine was present in the irradiated solution the method of isolation was as follows : The irradiated solutions were diluted with ether or benzene and washed with water (2 × 50 ml.), 2N-hydrochloric acid (3 × 50 ml.), water, and finally sodium hydrogen carbonate solution. To all the washings, combined, 2N-hydrochloric acid was added and the acidic degradation products were extracted with ether and estimated as before.

For estimation of aldehydic products, the residual acid-free solution was shaken with freshly prepared sodium hydrogen sulphite solution (75 ml.). The aqueous bisulphite layer, together with water-washings (2 × 20 ml.) of the organic layer, was mixed with an equal volume of saturated sodium carbonate solution and steam-distilled into dimedone or 2 : 4-dinitrophenylhydrazine reagent. After being kept overnight in the ice-chest, the aldehydic derivative was collected, washed, dried, and weighed.

The mean results of these determinations are recorded in Table 2. They are derived from at least four replicates. For the unsymmetrically substituted deoxybenzoins the weights of the 2 : 4-dinitrophenylhydrazones of the volatile aldehydes isolated are recorded; in other cases, the aldehydes were only identified.

After separation of the acidic and aldehydic components of the irradiated solutions, the other photolysis products were isolated from the neutral benzene solutions as described below.

Deoxybenzoin. The benzene solution (from 5 × 2 g. portions) was evaporated and the brown viscous residue was extracted with cold light petroleum. The insoluble resinous residue was purified by dissolution in benzene and precipitation with light petroleum. This process

[5] Jenkins, *J. Amer. Chem. Soc.*, 1935, **57**, 2733.
[6] Bretschneider and Ajtai, *Ber.*, 1941, **74**, 571; Fodor *et al.*, *Ber.*, 1941, **74**, 589; *J.*, 1948, 684.
[7] Green and Schoetzow, *J. Amer. Pharm. Assoc.*, 1933, **22**, 412.

TABLE 2. *Irradiation products* (Y = *p*-X·C_6H_4-; Y′ = *p*-X′·C_6H_4-).

Subst.			Irradn. in: CO_2		CO_2–C_5H_5N		Air		Air–C_5H_5N	
X	X′	R	Y·CHO	Y′·CO_2H	Y·CHO	Y′·CO_2H	Ar·CHO	Ar·CO_2H	Ar·CHO	Ar·CO_2H
H	H	H	3·24	0·69	1·52	1·24	2·25	18·14	1·72	33·23
OMe	H	H	1·27	0·20	1·75	0·64	4·20	4·92	2·80	14·98
OMe	OMe	H	3·73	0·68	0·34	3·43	3·00	19·72	1·99	40·05
H	NO_2	H	0·09	0·47	0·05	0·64	—	0·50	—	33·40
OMe	NO_2	H	0·09	0·52	0·06	0·88	—	1·50	—	36·95
H	H	Me	12·39	0·80	—	—	3·44	24·00	—	—
H	H	Et	11·38	0·72	—	—	3·44	21·77	—	—
OMe	OMe	Me	8·96	0·81	—	—	3·62	16·95	—	—
OMe	OMe	Et	7·93	0·85	—	—	3·71	15·20	—	—
H	H	Ph	9·59	0·79	—	—	2·60	18·68	—	—

was repeated several times until the resinous material was obtained as a yellowish-white amorphous powder (0·75 g.), m. p. 167—175° (decomp.) [Found: C, 85·4, 85·2; H, 5·6, 5·7. Calc. for $(C_{14}H_{11}O)_n$: C, 86·1; H, 5·6. Calc. for $(C_{14}H_{12}O)_n$: C, 85·7; H, 6·1%].

The light petroleum extract was evaporated at room temperature, yielding unchanged crystalline deoxybenzoin (7·5 g.) and an oil. The latter (1·59 g.) was further purified by treatment with cold light petroleum in which it is more soluble than deoxybenzoin. The oil gave, on distillation fractions (*a*) (0·4 g.) b. p. <120°/1·2 mm. and (*b*) b. p. 120—150°/1·2 mm. The former yielded dibenzyl which crystallised from ethanol in prismatic needles,[8] m. p. and mixed m. p. 52°.

Didesyl (0·1 g.) separated from the deoxybenzoin fraction on treatment with ice-cold ether in which it is sparingly soluble. It crystallised from benzene–light petroleum in prismatic needles,[9] m. p. and mixed m. p. 245° (Found: C, 86·1; H, 5·5. Calc. for $C_{28}H_{22}O_2$: C, 86·1; H, 5·6%), which gave a grass-green colour with concentrated sulphuric acid.[10]

The deoxybenzoin solutions which were irradiated in presence of air gave a positive peroxide test and did not yield dibenzyl or didesyl.

4-Methoxydeoxybenzoin,[11] 4 : 4′-dimethoxydeoxybenzoin.[12] 4′-nitrodeoxybenzoin,[13] and 4-methoxy-4′-nitrodeoxybenzoin[14] did not give photolysis products other than the aldehydes and acids recorded in the Table.

α-Phenylpropiophenone (I; X = X′ = H, R = Me).[15] The benzene solution (from 6 × 2 g. portions) left after separation of benzoic acid and benzaldehyde yielded a pale brown viscous residue which was extracted with cold light petroleum. The oil (3·5 g.) recovered from this extract was treated with ice-cold methanol, and the solution gave *meso*-2 : 3-diphenylbutane (0·9 g.) on slow evaporation. It crystallised from methanol in flakes,[16] m. p. and mixed m. p. 126° (Found: C, 91·1; H, 8·7. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%). (More *meso*-2 : 3-diphenylbutane was obtained as a sublimate when the residual oil was heated with traces of iodine for 6 hr. at 230—240°; under these conditions the oily 2 : 3-diphenylbutane, likely to be present, is converted into the racemic isomeride.[17]) The brown resinous residue which was insoluble in light petroleum was purified by treatment with benzene–light petroleum as before, yielding an amorphous solid, m. p. 163° (decomp.) (Found: C, 83·4; H, 6·0, 5·9%).

α-*Phenylbutyrophenone*.[15] The brown viscous residue recovered from the benzene solution was extracted with cold light petroleum. On slow evaporation the extract gave an odorous oil in about 30% yield with respect to the deoxybenzoin. It gave on distillation a fraction, b. p. 158—160°/1·2 mm., which did not solidify. *meso*-3 : 4-Diphenylhexane was obtained from the first fraction after the oily impurities had been removed with cold methanol. It crystallised from methanol in needles,[18] m. p. and mixed m. p. 91—92° (Found: C, 90·5; H, 9·35. Calc. for $C_{16}H_{18}$: C, 90·75; H, 9·25%).

[8] Alexander and Fuson, *J. Amer. Chem. Soc.*, 1936, **58**, 1745.
[9] Knoevenagel, *Ber.*, 1888, **21**, 1355.
[10] Fehrlin, *Ber.*, 1889, **22**, 553; Hahn and Murray, *J. Amer. Chem. Soc.*, 1914, **36**, 1489.
[11] Ney, *Ber.*, 1888, **21**, 2450.
[12] Stobbe, *Ber.*, 1902, **35**, 912.
[13] Petrenko-Kritschenko, *Ber.*, 1892, **25**, 2242.
[14] Rubin and Wishinsky, *J. Amer. Chem. Soc.*, 1944, **66**, 1948.
[15] Meyer and Oelker, *Ber.*, 1888, **21**, 1297.
[16] Haword, Hilbert, Wiebe, and Gaddy, *J. Amer. Chem. Soc.*, 1932, **54**, 3639.
[17] Lyepin, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1190.
[18] Fodor and Wein, *J.*, 1948, 686.

p-*Methoxy*-α-p′-*methoxyphenylpropiophenone*.[19] The neutral aldehyde-free residue recovered from the benzene solution (from 5 × 2 g. portions) was extracted with cold light petroleum. When this extract was evaporated at room temperature, an oil contaminated with *meso*-2 : 3-di-(*p*-methoxyphenyl)butane was obtained. On treatment with ice-cold methanol, the oil dissolved, leaving crystalline *meso*-2 : 3-di-(*p*-methoxyphenyl)butane (0·8 g.). It recrystallised from methanol in prismatic needles,[20] m. p. 136° (Found : C, 79·5; H, 8·2. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·2%). Racemic 2 : 3-di-(*p*-methoxyphenyl)butane was obtained from the methanolic solution of the oil, after separation of the *meso*-isomer, by dilution with water and extraction with ether. The residue which was recovered from the ethereal solution was dissolved in a minimum of ethanol and kept in the ice-chest; the racemic compound crystallised. It separated from methanol in flakes[20] (0·2 g.), m. p. 87° (Found : C, 79·6; H, 8·1%).

p-*Methoxy*-α-p′-*methoxyphenylbutyrophenone*.[19] The neutral anisaldehyde-free residue (from 9 × 2 g. portions), which was obtained as a pale brown viscous oil, was extracted with light petroleum, and the solution evaporated at room temperature. The oily residue (4·6 g.) which was contaminated with minute crystals was treated with ice-cold methanol in which the oil dissolved leaving *meso*-hexœstrol dimethyl ether (1·8 g.). This separated from methanol in prisms,[21] m. p. and mixed m. p. 144° (Found : C, 80·4; H, 8·8. Calc. for $C_{20}H_{26}O_2$: C, 80·5; H, 8·7%).

meso-αα-*Diphenylacetophenone*.[22] The benzaldehyde-free neutral benzene solution was concentrated and then carefully diluted with light petroleum; *sym*-tetraphenylethane separated in about 25% yield with respect to the original ketone. It crystallised from benzene–light petroleum in prisms,[23] m. p. and mixed m. p. 211° (Found : C, 93·3; H, 6·7. Calc. for $C_{26}H_{22}$: C, 93·4; H, 6·6%).

No photolysis products were obtained from *meso*-ααα-triphenylacetophenone and all the methylene-substituted deoxybenzoins irradiated in contact with dry air gave negative peroxide tests.

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Moharram Bey, Alexandria. [*Received, November 4th*, 1955.]

[19] Dodds and Goldberg, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140.
[20] Wessely, Bauer, Chwala, Plaichinger, and Schönbeck, *Monatsh.*, 1948, **79**, 596.
[21] Ajtai, *Ber.*, 1941, **74**, 582; Dodds, Goldberg, and Grunfeld, *Proc. Roy. Soc.*, 1944, *B*, **132**, 83.
[22] Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2051.
[23] Norris, Thomas, and Brown, *Ber.*, 1910, **43**, 2959.

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348. *Methylnicotinic Acids. Part I. Condensation of 2-Methyl-6-phenylnicotinic Acid and its Ethyl Ester with Aldehydes.*

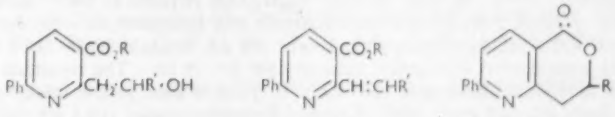
By E. Tittensor and D. G. Wibberley.

Condensation of benzaldehyde with 2-methyl-6-phenylnicotinic acid and its ethyl ester has been shown to produce a lactone in addition to the styryl derivatives of the acid and its ester. With certain substituted benzaldehydes, however, the lactone was the only product isolated.

Little information appears in the literature on the condensation of 2- or 4-methylnicotinic acid with aldehydes apart from a report by Koenigs [1] that 4-methylnicotinic acid condenses with formaldehyde and less readily with acetaldehyde when heated in a sealed tube, one of the products from the latter condensation being the lactone of 4-(2-hydroxy-*n*-propyl)nicotinic acid. Since 2-methyl-6-phenylnicotinic acid is readily prepared by Späth and Burger's method,[2] it was chosen as a suitable derivative with which to begin an investigation into these condensations. It was found, however, that under the conditions described by Koenigs no reaction took place between 2-methyl-6-phenylnicotinic acid and formaldehyde or acetaldehyde, but extension of the investigation to include aromatic aldehydes gave positive results. Heating 2-methyl-6-phenylnicotinic acid with benzaldehyde and water in a sealed tube yielded 2-(2-hydroxyphenethyl)-6-phenylnicotinic

[1] Koenigs, *Ber.*, 1901, **34**, 4336.
[2] Späth and Burger, *Monatsh.*, 1928, **49**, 265.

acid (I; R = H, R′ = Ph), whereas in acetic anhydride a mixture of 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) and 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (III; R = Ph) was obtained.



(I) (II) (III)

6-Phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) showed normal olefinic reactions towards bromine water and aqueous potassium permanganate. The lactone (III; R′ = Ph) was readily converted into the hydroxy-acid (I; R = H, R′ = Ph) in hot aqueous acetic acid, and re-formation of the lactone was accomplished by heating the acid with acetic anhydride or in a solvent such as ethyl acetate, some of the 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) being formed simultaneously. It is not possible, by heating alone, with acetic anhydride or with mineral acid, to convert 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) into the lactone (III; R′ = Ph). It thus seems clear that the first product of reaction between benzaldehyde and 2-methyl-6-phenylnicotinic acid, the hydroxy-acid (I; R = H, R′ = Ph), is converted during the reaction into a mixture of the styryl compound (II; R = H, R′ = Ph) and the lactone (III; R′ = Ph).

Substitution of ethyl 2-methyl-6-phenylnicotinate for the acid in reactions with benzaldehyde gave essentially similar results. The first product, ethyl 2-(2-hydroxyphenethyl)-6-phenylnicotinate (I; R = Et, R′ = Ph) was never isolated, but from condensations in sealed tubes under the influence of zinc chloride the major product was ethyl 6-phenyl-2-styrylnicotinate (II; R = Et, R′ = Ph) and was accompanied by the lactone (III; R′ = Ph) or in some experiments the hydroxy-acid (I; R = H, R′ = Ph). Ethyl 6-phenyl-2-styrylnicotinate (II; R = Et, R′ = Ph) and the lactone (III; R = Ph) were also produced when acetic anhydride was used as a condensing reagent and a very small quantity of 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) was recovered from the mother-liquors from several experiments.

The crude yields in condensations of substituted benzaldehydes with 2-methyl-6-phenylnicotinic acid and its ethyl ester in acetic anhydride were in the expected order p-NO_2 > m-NO_2 > H > p-MeO > o-OH. p-Nitrobenzaldehyde yielded the lactone (III; R′ = p-NO_2·C_6H_4) only, but both the stilbazole (II; R = H) and the lactone were obtained where R′ = m-NO_2·C_6H_4. p-Anisaldehyde and salicylaldehyde yielded, apart from intractable material, only the lactones (III; R′ = p-MeO·C_6H_4, R′ = o-HO·C_6H_4) and unchanged starting material in condensations with the ethyl ester. With the free acid salicylaldehyde yielded no product and p-acetamidobenzaldehyde gave only dark tars from reactions with both the acid and its ethyl ester.

Experimental

Condensation of 2-Methyl-6-phenylnicotinic Acid and Benzaldehyde.—(a) *In the presence of water.* 2-Methyl-6-phenylnicotinic acid (0·75 g.), benzaldehyde (0·3 c.c.), and water (0·2 c.c.) were heated in a sealed tube at 180° for 10 hr. The product was stirred with water and dissolved in the minimum of hot aqueous ethanol (1 : 1), to yield 2-(*2-hydroxyphenethyl*)-6-*phenylnicotinic acid* (I; R = H, R′ = Ph) (0·5 g.) which, on recrystallisation from aqueous ethanol, formed colourless needles, m. p. 176—177° (Found: C, 74·9; H, 4·7; N, 4·3. $C_{20}H_{17}O_2N$ requires C, 75·2; H, 5·3; N, 4·4%).

(b) *In the presence of acetic anhydride.* 2-Methyl-6-phenylnicotinic acid (4·26 g.), benzaldehyde (2·21 c.c.), and acetic anhydride (1·88 c.c.) were refluxed for 8 hr. Water (20 c.c.) was added and the gum which separated was stirred with ethanol (20 c.c.), to yield the crude product (4·1 g.), m. p. 132—147°. This crude product was boiled with ethanol (70 c.c.), the mixture cooled rapidly and the insoluble 2-(*2-hydroxyphenethyl*)-6-*phenylnicotinic lactone* (1·3 g.), m. p. 188—190°, collected. Recrystallisation from ethanol gave colourless plates, m. p. 194—195°

(Found: C, 79·5; H, 5·0; N, 4·9. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%). The filtrate was concentrated to 25 c.c., to yield *6-phenyl-2-styrylnicotinic acid* (0·95 g.), m. p. 189—191°. Recrystallisation from benzene and then ethanol gave colourless prisms, m. p. 202—203° (Found: C, 79·7; H, 5·3; N, 4·7. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%).

Condensation of Ethyl 2-Methyl-6-phenylnicotinate and Benzaldehyde.—(a) *In the presence of zinc chloride.* Ethyl 2-methyl-6-phenylnicotinate (24 g.), benzaldehyde (15·2 c.c.), and zinc chloride (6·8 g.) were heated in a sealed tube at 180° for 18 hr. The resultant brown oil was triturated with 2N-hydrochloric acid (100 c.c.), to yield a pale yellow sticky solid which on crystallisation from ethanol gave *ethyl 6-phenyl-2-styrylnicotinate* (13·5 g.), m. p. 100—102°. Recrystallisation from ethanol gave colourless needles, m. p. 106—107° (Found: C, 80·0; H, 5·7; N, 4·7. $C_{22}H_{19}O_2N$ requires C, 80·2; H, 5·8; N, 4·3%). Concentration of the mother-liquors gave a second crop which on recrystallisation from ethanol and ethyl acetate gave the lactone (3·1 g.), m. p. 194—195°.

(b) *In the presence of acetic anhydride.* Ethyl 2-methyl-6-phenylnicotinate (9·6 g.), benzaldehyde (5·1 g.), and acetic anhydride (4·5 g.) were refluxed for 10 hr. The solution was cooled and stirred with 2N-hydrochloric acid. Basification of the acid layer yielded ethyl 2-methyl-6-phenylnicotinate (3·4 g.), m. p. 44—46°. The residual sticky solid was stirred with water and then with alcohol, to give a crude product (4·5 g.), m. p. 98—128°, which was dissolved in the minimum of hot ethanol and cooled rapidly, to yield 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (1·2 g.), m. p. 194—195°. The filtrate after concentration yielded ethyl 6-phenyl-2-styrylnicotinate (1·9 g.), m. p. 106—107°.

Reaction of the Hydroxy-acid (I; R = H, R′ = Ph) *with Acetic Anhydride.*—2-(2-Hydroxyphenethyl)-6-phenylnicotinic acid (1·0 g.) was refluxed with acetic anhydride (10 c.c.) for 2·5 hr. The mixture was cooled and boiled with ethanol (20 c.c.) and the solvents were evaporated, to leave a product (0·95 g.), m. p. 178—187°, which, recrystallised from ethanol, yielded 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (0·26 g.), m. p. and mixed m. p. 194—195°. The alcohol was distilled from the filtrate, and the residue recrystallised from ethyl acetate, to give 6-phenyl-2-styrylnicotinic acid (0·29 g.), m. p. and mixed m. p. 202—203°.

Reaction of the Lactone (III; R′ = Ph) *with Aqueous Acetic Acid.*—2-(2-Hydroxyphenethyl)-6-phenylnicotinic lactone (0·5 g.) was refluxed with acetic acid–water (4 : 1; 10 c.c.) for 1 hr. and the solution left for 4 days. The crude product which separated was collected and recrystallised from aqueous alcohol, to give 2-(2-hydroxyphenethyl)-6-phenylnicotinic acid (0·34 g.), m. p. and mixed m. p. 176—177°.

Condensation of 2-Methyl-6-phenylnicotinic Acid and its Ethyl Ester with Substituted Benzaldehydes.—(a) p-*Nitrobenzaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), *p*-nitrobenzaldehyde (1·8 g.), and acetic anhydride (1·1 g.) were heated together for 8 hr. at 170—180°. The resulting semi-solid residue was stirred with 2N-hydrochloric acid, to give the crude product (3·6 g.), m. p. 208—212°. Crystallisation from ethyl acetate and from ethanol yielded *2-(2-hydroxy-4′-nitrophenethyl)-6-phenylnicotinic lactone* (III; R′ = *p*-NO_2·C_6H_4) (1·67 g.) as yellow needles, m. p. 237—239° (Found: C, 69·1; H, 3·6; N, 8·4. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·0; N, 8·1%).

2-Methyl-6-phenylnicotinic acid (4·3 g.), *p*-nitrobenzaldehyde (3·6 g.), and acetic anhydride (2·0 g.) were heated together under reflux for 6 hr. at 200—210°. The mixture, which had solidified after the first 2 hr., was allowed to cool and then ground with water (20 c.c.), and the crude 2-(2-hydroxy-4′-nitrophenethyl)-6-phenylnicotinic lactone (III; R′ = *p*-NO_2·C_6H_4) (6·8 g.), m. p. 220—224°, collected. Crystallisation from ethanol yielded yellow needles (5·9 g.), m. p. and mixed m. p. 237—239°.

(b) m-*Nitrobenzaldehyde.* 2-Methyl-6-phenylnicotinic acid (12·8 g.), *m*-nitrobenzaldehyde (10·0 g.), and acetic anhydride (6·0 g.) were refluxed for 8 hr. The semi-solid residue was ground with water (50 c.c.), filtered, washed with ethanol (20 c.c.), and then dissolved in the minimum of hot ethanol (600 c.c.). The solution was cooled rapidly, to give *2-(2-hydroxy-3′-nitrophenethyl)-6-phenylnicotinic lactone* (III; R′ = *m*-NO_2·C_6H_4) (7·3 g.), m. p. 178—181°. Recrystallisation from ethanol gave 6·4 g., m. p. 178—179° (Found: C, 69·1; H, 3·9; N, 8·4%). The filtrate was concentrated to 200 c.c. and left for several hours, to yield *2-3′-nitrostyryl-6-phenylnicotinic acid* (II; R = *m*-NO_2·C_6H_4) (7·95 g.), m. p. 201—204°. Recrystallisation from ethyl acetate gave 6·4 g., m. p. 209—210° (Found: C, 69·7; H, 4·2; N, 8·2. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·0; N, 8·1%).

The lactone and stilbazole were also obtained in lower yields (21·7 and 9·8% respectively) in a similar condensation of ethyl 2-methyl-6-phenylnicotinate.

(c) p-*Anisaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), *p*-anisaldehyde (1·7 g.),

and acetic anhydride (1·1 g.) were refluxed for 8 hr. The residual brown oil was dissolved in ether, and the ether solution extracted with 2N-hydrochloric acid. Basification of the acid extract yielded ethyl 2-methyl-6-phenylnicotinate (1·9 g.). 2-(*2-Hydroxy-4′-methoxyphenethyl*)-*6-phenylnicotinic lactone* (III; R′ = *p*-MeO·C_6H_4) (0·23 g.), m. p. 155—157°, separated gradually from the ether extract. Recrystallisation from butan-1-ol gave colourless plates, m. p. 170·5—171·5° (Found: C, 75·6; H, 5·2; N, 4·4. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1; N, 4·2%).

The same product was also obtained in higher yield (14%) in a condensation of 2-methyl-6-phenylnicotinic acid.

(d) *Salicylaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), salicylaldehyde (1·46 g.), and acetic anhydride (1·0 g.) were heated at 180° for 8 hr. 2N-Hydrochloric acid (20 c.c.) was added and the insoluble dark brown oil extracted into ether. The acid extract was basified, giving ethyl 2-methyl-6-phenylnicotinate (0·9 g.). The ether extract was concentrated to give a brown oil (1·92 g.) which on trituration with methanol yielded 2-(*2-hydroxy-2′-hydroxyphenethyl*)-*6-phenylnicotinic lactone* (0·4 g.), m. p. 91—94°, and on recrystallisation from ethanol gave plates, m. p. 98—99° (Found: C, 75·5; H, 5·3; N, 4·4. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·7; N, 4·4%).

Ethyl 2-(1 : 2-*Dibromophenethyl*)-*6-phenylnicotinate.*—Bromine (0·9 g.) was added to a solution of ethyl 6-phenyl-2-styrylnicotinate (1·6 g.) in acetic acid (20 c.c.). Decoloration was almost immediate; the mixture was refluxed for 0·5 hr. and left for 3 days; the product (0·65 g.), m. p. 176—178° (decomp.), was then collected. The filtrate was diluted with water and extracted with ether, and the ether evaporated to yield, after trituration with alcohol, crude unchanged ethyl 6-phenyl-2-styrylnicotinate. The solid *ester*, m. p. 176—178°, was recrystallised from ethanol, to give colourless prisms, m. p. 180—182° (Found: N, 3·0; Br, 30·7. $C_{32}H_{19}O_2NBr_2$ requires N, 2·9; Br, 32·8%).

The Technical College, Nottingham. [*Received, December 19th*, 1955.]

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349. *Oxazolopyridines and Oxazoloquinolines. Part I. 2′-Alkyl and 2′-Aryl Derivatives of Oxazolo(4′ : 5′-3 : 4)pyridine and Oxazolo(4′ : 5′-3 : 4)quinoline.*

By James Fraser and E. Tittensor.

The synthesis and some reactions of oxazolo(4′ : 5′-3 : 4)pyridines and oxazolo(4′ : 5′-3 : 4)quinolines are described.

In an attempt to synthesise 2′-substituted oxazolo(4′ : 5′-3 : 4)pyridines and oxazolo-(4′ : 5′-3 : 4)quinolines the standard methods used in the benzoxazole series, *viz.*, heating *o*-hydroxy-amines with amides, nitriles, carboxylic acids, esters, or acid chlorides, proved of no value. Equally unsuccessful were attempts at cyclodehydration of hydroxy-acylamino-compounds by phosphoryl chloride, the yields being extremely poor. Extension of the method generally used for 2-methylbenzoxazoles, 2′-methyloxazolo(5′ : 4′-2 : 3)pyridines,[1,2] and 2′-methyloxazolo(4′ : 5′-3 : 4)quinolines,[3] namely, refluxing *o*-hydroxy-amines in acetic anhydride, to the use of a variety of aliphatic and aromatic acid anhydrides, gave moderately good yields of the desired oxazolopyridines and oxazoloquinolines. It has not been possible to prepare the parent compounds, for although 3-amino-4-hydroxy-pyridine and -quinoline both yield formamido-derivatives in refluxing formic acid, these have not yet been cyclised. The oxazolo(4′ : 5′-3 : 4)-pyridines and -quinolines are solids, the 2′-alkyl derivatives having a characteristic odour. They readily form crystalline monomethiodides. At room temperature 2′-methyloxazolo(4′ : 5′-3 : 4)pyridine is hydrolysed rapidly by N-hydrochloric acid but it is stable to water and aqueous sodium hydroxide. Unlike 2-methylbenzoxazole it is also stable to boiling water and in this resembles 2-methyl-5- and 2-methyl-7-nitrobenzoxazole which according to Phillips [4] can be recrystallised from hot water containing a little acetic acid.

[1] Saikachi, *J. Pharm. Soc. Japan*, 1944, **64**, 201.
[2] Yamamoto and Takahashi, *ibid.*, 1951, **71**, 169.
[3] Bachman, Welton, Jenkins, and Christian, *J. Amer. Chem. Soc.*, 1947, **69**, 370.
[4] Philips, *J.*, 1930, 2685.

Skraup *et al.*[5,6] observed that 2-methylbenzoxazole condensed with benzaldehyde although they did not characterise the product. They also found that it did not react with dimethyl-*p*-nitrosoaniline, nitrous acid, or diazonium salts, and that it was oxidised by aqueous potassium permanganate to benzoxazole-2-carboxylic acid. 2′-Methyloxazolo(4′ : 5′-3 : 4)pyridine condenses with benzaldehyde to give a styryl derivative. It is decomposed by aqueous potassium permanganate and does not react with the other reagents mentioned. Attempts to oxidise the 2′-methyl group by means of selenium dioxide or to convert it into a bromomethyl group by means of *N*-bromosuccinimide failed.

Improved syntheses of 3-amino-4-hydroxy-pyridine and -quinoline, in which reduction was best accomplished by hydrogenation of the corresponding nitro-compounds by palladised charcoal, are described.

Experimental

3-Amino-4-hydroxyquinoline.—A suspension of 4-hydroxy-3-nitroquinoline (3 g.) and 10% palladised charcoal (1 g.) in methanol (100 c.c.) was shaken with hydrogen at atmospheric pressure until absorption ceased. Removal of the catalyst and evaporation under reduced pressure in an atmosphere of nitrogen gave the light-brown product (2·4 g.) which was used without further purification. The acetyl derivative had m. p. 283—284° (Ochiai and Ogura [7] give m. p. 285°).

3-Amino-4-hydroxypyridine.—4-Hydroxy-3-nitropyridine (10 g.) was reduced as above in methanol (100 c.c.), with 10% palladised charcoal (1 g.). The product was obtained as colourless or pale purple prisms (7·4 g.) which oxidised in air. The *monoacetyl derivative*, m. p. 213—214°, formed colourless needles from aqueous acetone (Found: C, 49·7; H, 6·1; N, 16·8. $C_7H_8O_2N_2,H_2O$ requires C, 49·4; H, 5·9; N, 16·5%).

Preparation of 2′-Alkyloxazolo(4′ : 5′-3 : 4)-pyridines and -quinolines.—A mixture of 3-amino-4-hydroxy-pyridine or -quinoline (0·04 mole) and the acid anhydride (0·2—0·3 mole) was refluxed for 24 hr., cooled, and stirred with ice-water (300 c.c.). The solution was basified by aqueous sodium hydroxide with cooling, and extracted with benzene (6 × 50 c.c.). The combined extracts were washed with saturated aqueous sodium chloride (20 c.c.) and dried (Na_2SO_4). Evaporation under reduced pressure gave a coloured product which was crystallised (charcoal) from light petroleum (b. p. 40—60°). The *products* are tabulated.

Table 1. *Products.*

No.	2′-Subst.	Yield (%)	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
				Oxazolo(4′ : 5′-3 : 4)pyridines.						
1	Me [a]	27	57·5—59°	$C_8H_6ON_2$	62·7	4·7	20·6	62·7	4·5	20·9
2	Et [a]	32	46—7	$C_9H_8ON_2$	64·8	5·6	18·9	64·9	5·4	18·9
3	Pr^n [a]	42	72·5—73·5	$C_{10}H_{10}ON_2$	66·8	6·3	17·5	66·7	6·2	17·3
4	Ph [b]	45	123·5—4·5	$C_{12}H_8ON_2$	73·4	4·1	14·4	73·4	4·1	14·3
5	*p*-C_6H_4Me [b]	57	179·5—180	$C_{13}H_{10}ON_2$	74·5	4·7	13·5	74·3	4·8	13·3
6	*p*-MeO·C_6H_4 [b]	53	177—178	$C_{13}H_{10}O_2N_2$	69·1	4·4	12·5	69·0	4·4	12·4
7	*p*-C_6H_4Cl [b]	32	157—158	$C_{12}H_7ON_2Cl$	62·8	3·0	12·3	62·5	3·0	12·1
				Oxazolo(4′ : 5′-3 : 4)quinolines.						
8	Me [a]	75	90—91	$C_{11}H_8ON_2$	—	—	15·3	—	—	15·2
9	Et [a]	72	72·5—73·5	$C_{12}H_{10}ON_2$	72·6	5·2	14·1	72·8	5·1	14·1
10	Pr^n [b]	45	69—70	$C_{13}H_{12}ON_2$	73·3	5·8	13·1	73·6	5·7	13·2
11	Ph [a]	63	168—169	$C_{16}H_{10}ON_2$	78·0	4·1	13·4	77·8	4·1	11·4
12	*p*-C_6H_4Me [b]	42	216—218	$C_{17}H_{12}ON_2$	78·7	4·7	10·8	78·5	4·6	10·8
13	*p*-MeO·C_6H_4 [b]	40	188—189	$C_{17}H_{12}O_2N_2$	73·7	3·9	10·3	73·9	4·3	10·1
14	*p*-C_6H_4Cl [b]	86	219·5—220·5	$C_{16}H_9ON_2Cl$	68·6	3·2	9·8	68·4	3·2	10·0

[a] Needles. [b] Prisms.

Preparation of 2′-Aryloxazolo(4′ : 5′-3 : 4)-pyridines and -quinolines.—A mixture of 3-amino-4-hydroxy-pyridine or -quinoline (0·01 mole) and the acid anhydride (0·03 mole) was heated rapidly to 300° in a flask fitted with a wide air-condenser and the temperature kept thereat for

[6] Skraup and Böhm, *Ber.*, 1926, **59**, 1007.
[6] Skraup and Moser, *Ber.*, 1922, **55**, 1080.
[7] Ochiai and Ogura, *J. Pharm. Soc. Japan*, 1952, **72**, 767.

15 min. The cooled melt was dissolved in benzene (200 c.c.) and extracted with ice-cold 2N-hydrochloric acid (3 × 20 c.c.). The combined extracts were filtered and basified with aqueous sodium hydroxide. The white precipitate was collected and crystallised from acetone. *Products* are tabulated.

TABLE 2. *Derivatives.*

Methiodide of No.	M. p.	Solvent	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
1	147—148° [b]	A	$C_8H_9ON_2I$	35·1	3·4	10·2	34·8	3·3	10·1
2	146—147 [a]	A	$C_9H_{11}ON_2I$	37·3	4·0	9·6	37·2	3·8	9·7
3	94—96·5 [a]	A	$C_{10}H_{13}ON_2I$	—	—	—	—	—	—
4	279—280 [b]	B	$C_{12}H_{13}ON_2I$	46·5	3·4	8·3	46·2	3·3	8·3
5	226—227·5 [b]	B	$C_{14}H_{13}ON_2I$	47·3	3·6	7·7	47·7	3·7	8·0
6	234—235·5 [b]	B	$C_{14}H_{13}O_2N_2I$	—	—	—	—	—	—
7	267·5—268·5 [b]	B	$C_{13}H_{10}ON_2ClI$	42·4	2·6	7·6	41·9	2·7	7·5
8	252·5—253·5 [a]	B	$C_{13}H_{11}ON_2I$	44·3	3·5	8·8	44·2	3·4	8·6
9	216—217 [a]	B	$C_{12}H_{13}ON_2I$	46·3	3·9	8·3	45·9	3·8	8·2
10	193—194 [a]	B	$C_{14}H_{15}ON_2I$	47·6	4·1	7·5	47·5	4·2	7·9
11	260—261 [b]	C	$C_{17}H_{13}ON_2I$	52·2	3·2	7·5	52·5	3·4	7·2
12	238—240 [b]	C	$C_{13}H_{15}ON_2I$	53·9	3·6	7·1	53·7	3·7	7·0
13	251—252 [b]	C	$C_{16}H_{15}O_2N_2I$	51·9	3·4	6·7	51·7	3·6	6·7
14	250—251 [b]	C	$C_{17}H_{12}ONClI$	48·2	2·8	6·7	48·3	2·8	6·6
Picrate of No.									
3	130—131 [a]	B	$C_9H_{10}ON_2.C_6H_3O_7N_3$	46·3	3·4	17·8	46·0	3·3	17·9
6	251—252 [a]	B	$C_{12}H_{10}O_2N_2.C_6H_3O_7N_3$	50·3	3·1	15·3	50·1	2·9	15·4

A, alcohol–ether; B, absolute alcohol; C, aq. alcohol. [a] Needles. [b] Prisms.

Hydrolysis of 2′-Methyloxazolo(4′ : 5′-3 : 4)pyridine.—A solution of the oxazole (0·3 g.) in N-hydrochloric acid (4·0 c.c.) was kept at 25° for 2 hr. On basification with aqueous sodium hydroxide and extraction with ether unchanged oxazole (0·01 g.) was recovered. The aqueous layer was neutralised with acetic acid and cooled in ice, giving 3-acetamido-4-pyridone (needles; 0·1 g.), m. p. and mixed m. p. 213—214°.

The oxazole was recovered from refluxing aqueous solution after 30 min.

2′-Styryloxazolo(4′ : 5′-3 : 4)pyridine.—2′-Methyloxazolo(4′ : 5′-3 : 4)pyridine (0·5 g.), freshly distilled benzaldehyde (3 c.c.), and zinc chloride (0·3 g.) were refluxed for 5 hr. (bath at 170°). The mixture was diluted with benzene (20 c.c.) and extracted with 2N-hydrochloric acid (2 × 10 c.c.), and the combined acid layers were basified with sodium hydroxide. The resulting yellow precipitate was recrystallised from aqueous acetone, to give colourless needles (0·06 g.), m. p. 122—123° (Found: C, 76·0; H, 4·7; N, 12·9. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

Cyclisation of 3-Benzamido-4-hydroxyquinoline by Phosphoryl Chloride.—3-Benzamido-4-hydroxyquinoline [8] (0·56 g.) was refluxed with phosphoryl chloride (10 c.c.) for 2 hr. The excess of chloride was evaporated under reduced pressure, and the residue, a very viscous liquid, was treated with ice-water and basified with aqueous sodium hydroxide. The mass gradually solidified, and after 3 hr. was collected. Crystallisation from acetone gave 2′-phenyloxazolo(4′ : 5′-3 : 4)quinoline (0·1 g.), m. p. 168—169°.

3-Amino-4-hydroxy-2 : 8-dimethylquinoline Hydrochloride.—4-Hydroxy-2 : 8-dimethylquinoline (10 g.) was dissolved in warm 5N-sodium hydroxide (100 c.c.), and the solution diluted with water (20 c.c.) and cooled to 5°. A solution of benzenediazonium chloride, made from aniline (6 g.), was added slowly and with stirring, the temperature being kept below 5°; the mixture was then made neutral by addition of ice-cold 5N-hydrochloric acid. The resulting copious red precipitate was collected, washed with water, and dried in a vacuum-desiccator. The crude dry phenylazo-derivative was heated for 2 hr. on a steam-bath with concentrated hydrochloric acid (200 c.c.) and stannous chloride (26 g.). After cooling, the yellow precipitate was collected, dissolved in hot water, and freed from tin by treatment with hydrogen sulphide and filtration. Evaporation of the filtrate to about 300 c.c. and keeping at 0° gave colourless needles of 3-amino-4-hydroxy-2 : 8-dimethylquinoline hydrochloride (7·0 g.). The *acetyl derivative*, prepared by adding acetic anhydride followed by sodium acetate to an aqueous solution of the hydrochloride, crystallised from aqueous ethanol as needles, m. p. 313·5—314° (Found: C, 62·7; H, 6·3; N, 11·4. $C_{13}H_{14}O_2N_2,H_2O$ requires C, 62·9; H, 6·5; N, 11·3%).

2′ : 2 : 8-Trimethyloxazolo(4′ : 5′-3 : 4)quinoline.—3-Amino-4-hydroxy-2 : 8-dimethylquinoline hydrochloride (1·89 g.) was refluxed with acetic anhydride (30 c.c.) and anhydrous sodium

[8] Musajo, *Gazzetta*, 1937, **67**, 222.

acetate (1·2 g.) for 4 hr. By using the general method of isolation described above for 2'-alkyloxazolo-derivatives, 2' : 2 : 8-*trimethyloxazoloquinoline* was obtained as pale-yellow needles (1·6 g.), m. p. 83—84° (Found: C, 74·0; H, 5·7; N, 13·0. $C_{13}H_{13}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%).

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350. *The Structure and Reactions of Dinitrogen Tetroxide.**

By ZOLTÁN G. SZABÓ, LAJOS G. BARTHA, and BÉLA LAKATOS.

A study of the reaction between dinitrogen tetroxide and iodide ions as a function of the iodide-ion concentration, temperature, and pressure shows that, in addition to the symmetrical $O_2N{\cdot}NO_3$ and its monomer, a tetroxide of another structure is present. Structural, kinetic, and energetic considerations unequivocally show that this tetroxide is the ring molecule suggested by Longuet-Higgins. The results include evidence that an equilibrium occurs between the three types of molecule (see Scheme A).

The other structure which may play a role in the formation of the tetroxide (II), *viz.*, nitrosonium nitrate, can be regarded only as an intermediate state. From the Longuet-Higgins molecule nitrosonium and nitrate ions can be formed *via* the nitrosonium nitrate (see Scheme B, p. 1793).

On the other hand, on interaction of NO^+ and NO_3^- ions nitrosonium nitrate is formed and ring closure gives the Longuet-Higgins molecule.

Concerning the kinetics of the reaction it has been concluded that the nitrogen dioxide dissociated from the tetroxide (I) determines the velocity of the transformation in the following two steps:

$$NO_2 + N_2O_4 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ONO_2{\cdot}NO + NO_2; \quad NO_2 + I^- \xrightarrow{k_2} NO_2^- + \tfrac{1}{2}I_2$$

The former reaction shows the tetroxide molecule (II) to be formed *via* the intermediate (III) which dissociates as shown (p. 1790). The high concentration of the tetroxide (II) (31% at 0°) favours the formation of Longuet-Higgins's type of molecule again rather than of nitrosonium nitrate, as no appreciable dipole moment can be detected.

THE consistent interpretation of experimental data obtained for the physical and chemical properties of dinitrogen tetroxide was rendered extremely difficult by the discrepancy between the symmetrical structure (I) established on the basis of physical measurements [1] and the conclusions drawn from chemical reactions,[2] according to which the structure of dinitrogen tetroxide can only be one from which the ions NO^+ and NO_3^-, on the one hand, and NO_2^+ and NO_2^-, on the other, can be simultaneously derived.

In order to reconcile the physical and chemical properties of dinitrogen tetroxide, Addison and Lewis [1c] and also Seel *et al.*[2c] assumed an equilibrium between the symmetrical

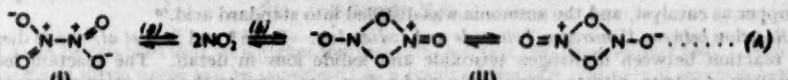
* Read, in abstract, at the First Hungarian Physicochemical Meeting, Szeged, 1954; *cf. Magyar Kém. Folyóirat*, 1955, **61**, 161.

[1] Röntgen spectra: Broadly and Robertson, *Nature*, 1949, **164**, 915. Infrared and Raman spectra: *e.g.*, (*a*) Sutherland, *Proc. Roy. Soc.*, 1933, *A*, **141**, 342; Harris and King, *J. Chem. Phys.*, 1934, **2**, 51, 321; (*b*) Perkins and Wilson, *Phys. Rev.*, 1932, **39**, 755. Dipole moment: *e.g.*, (*c*) Addison and Lewis, *J.*, 1953, 1809. Specific heat: (*d*) Giauque and Kemp, *J. Chem. Phys.*, 1938, **6**, 40. Specific conductivity: (*e*) Addison, Allen, Bolton, and Lewis, *J.*, 1951, 1288.

[2] With metals: *e.g.*, (*a*) Addison *et al.*, *J.*, 1949, S211, and subsequent papers. With halides: (*b*) Seel *et al.*, *Z. anorg. Chem.*, 1950, **261**, 75, and subsequent papers. With azides: (*c*) Seel, Nógrádi, and Breit, *ibid.*, 1952, **269**, 102. Hydrolysis and alcoholysis: *e.g.*, (*d*) Denbigh and Prince, *J.*, 1947, 790; Yoffe and Gray, *J.*, 1951, 1412. With metal oxides, hydroxides, and carbonates: *e.g.*, (*e*) Addison and Lewis, *J.*, 1953, 1319, 1874. With olefins: (*f*) Levy and Scaife, *J.*, 1946, 1093; 1948, 52. Formation of N_2O_5 from nitrosonium and nitronium salts: *e.g.*, Seel, *loc. cit.*; (*g*) Exner, *J.*, 1872, 1072. Electrolysis in presence of ionic partner: (*h*) Angus, Jones, and Phillips, *Nature*, 1949, **164**, 433. (*i*) With labelled alkylammonium nitrates: Clusius and Vecchi, *Helv. Chim. Acta*, 1953, **36**, 930.

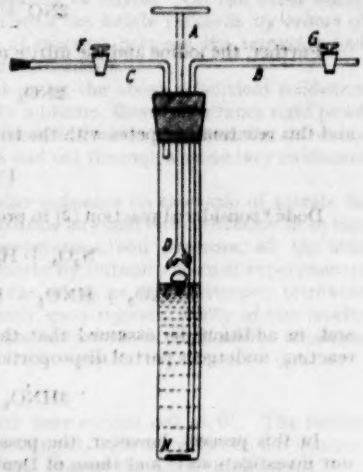
tetroxide favoured by physical methods, the ring structure proposed by Longuet-Higgins,[3] and nitrosyl nitrate.[4]

During the present investigations direct experimental evidence has been found for the existence of such equilibrium for the liquid dinitrogen tetroxide :



On the basis of kinetic measurements we conclude that tetroxide (II) arises through the intermediate nitrosonium nitrate and may be identified with the structure suggested by Longuet-Higgins. The dependence of the reaction between dinitrogen tetroxide and iodide ions in aqueous solution on iodide-ion concentration, temperature, and pressure has been examined, it being thought that the foregoing equilibrium, if real, would be very sensitive to such variations. Indeed, depending on the parameters referred to above, various amounts of nitrate, nitrite, iodine, and nitric oxide have been determined.

Fig. 1.



Experimental

Apparatus and Technique.—The reaction vessel was a 40 × 4 cm. glass tube (Fig. 1), the open end of which was closed by a three-bored rubber plug after it had been filled with the required quantities of reactants. In the middle bore of the plug a glass rod (*A*) was inserted, the lower end of which terminated in four claw-like points (*D*). This rod served for breaking the phial (*E*) containing the dinitrogen tetroxide. The claws pushed the phial forward, preventing it from emerging over the liquid surface. The two outside bores were used for inserting glass tubes each fitted with a tap. Tube *B*, by means of which nitrogen was previously passed through the system, reached to the bottom of the reaction vessel. Tube *C*, reaching about 1 cm. into the vessel, was employed for collecting the nitric oxide evolved after the reaction was over.

Klemenc and Rupp's method[5] was used for preparing dinitrogen tetroxide, the liquid being distilled into glass globes of about 1·5 cm. diameter, which were then sealed.

The reaction vessel, containing 250 ml. of potassium iodide solution of a chosen concentration,[6] and equipped with the phial containing the tetroxide, was placed in a bath at the required temperature, and then nitrogen was passed through the system for 2 hr. After simultaneous closure of taps *F* and *G*, the tube used for introducing nitrogen was drawn up above the liquid surface. After this, with constant stirring, the phial with the dinitrogen tetroxide was broken by rapidly pushing down the glass rod. Stirring was effected by a small electromagnetic stirrer *H*.

When reaction was complete, the iodine, nitrate, nitrite, and nitric oxide contents of the mixtures were determined.

After the tube *C* had been attached by means of ground joints to ½ l. gas-analytical test-tubes,[6] previously evacuated, the nitric oxide was collected by opening tap *F*. Then 3% hydrogen peroxide solution was poured into the 3 or 4 test-tubes containing nitric oxide to oxidize it to nitric acid, which was determined alkalimetrically.[7]

[6] The concentration of potassium iodide solution is throughout given in g. per 100 ml. of solution.

[3] Longuet-Higgins, *Nature*, 1947, **159**, 743.
[4] Addison, Lewis, and Thompson, *J.*, 1951, 2838.
[5] Klemenc and Rupp, *Z. anorg. Chem.*, 1930, **194**, 51.
[6] Szabó, *Z. analyt. Chem.*, 1943, **126**, 219.
[7] Moser, *ibid.*, 1911, **50**, 428; Szabó and Barthis, *Analyt. Chim. Acta*, 1952, **6**, 416.

Iodine was determined by titration with sodium thiosulphate.

Nitrate and nitrite were determined by decomposing the nitrite in a portion of the solution by boiling diluted sulphuric acid, and then the nitrate remaining unchanged was determined. In another sample the contents of both were determined together. In the two determinations both the nitrate and the nitrite were reduced to ammonia by ferrous hydroxide in the presence of copper as catalyst, and the ammonia was distilled into standard acid.[7a]

Reaction between Dinitrogen Tetroxide and Iodide Ion.—Dodé [8] and Seel *et al.*[2b] have discussed the reaction between dinitrogen tetroxide and iodide ions in detail. The reaction leads to formation of nitrite, nitrate, nitric oxide, and iodine, according to the two principal processes:

$$N_2O_4 + 2I^- \longrightarrow 2NO_2^- + I_2 \quad . . . . . (1)$$

$$N_2O_4 + I^- \longrightarrow NO_3^- + NO + \tfrac{1}{2}I_2 \quad . . . . . (2)$$

From the two studies it became evident that during and after these two principal reactions, other processes occur. Nitric oxide, liberated according to (2), reacts with unchanged dinitrogen tetroxide to give dinitrogen trioxide:

$$2NO + N_2O_4 \longrightarrow 2N_2O_3 \quad . . . . . (3)$$

Further, the iodine and the nitrite react thus:[9]

$$2NO_2^- + \tfrac{1}{2}I_2 \rightleftharpoons NO_3^- + NO + I^- \quad . . . . . (4)$$

and this reaction competes with the tri-iodide equilibrium (5) for the iodine:

$$I^- + I_2 \rightleftharpoons I_3^- \quad . . . . . (5)$$

Dodé [8] considered reaction (2) to proceed, not directly, but through hydrolysis:

$$N_2O_4 + H_2O = HNO_3 + HNO_2 \quad . . . . . (6)$$

$$HNO_2 + HNO_3 + KI = KNO_3 + NO + \tfrac{1}{2}I_2 + H_2O \quad . . . . (7)$$

and, in addition, he assumed that the nitrous acid formed during hydrolysis, before further reacting, undergoes partial disproportionation:

$$3HNO_2 = HNO_3 + 2NO + H_2O \quad . . . . . (8)$$

In this process, however, the possibility of hydrolysis must be excluded for, according to our investigations [10] and those of Denbigh and Prince,[2d] this hydrolysis is much too slow to be of significance here. The great difference between these two rates of reaction has already been mentioned by Prahl and Raschig,[11] and, moreover, in discussing an analogous reaction involving the NO_2–NO mixture and alkaline potassium iodide, they proved that hydrolysis does not play any role in the process. Our investigations on the dependence of hydrolysis on temperature and pressure [10] also undoubtedly prove these relationships. According to our further experimental evidence, hydrolysis occurs only if 1 mole of the tetroxide reacts with less than 1 g.-ion of the iodide.

Finally, under the same experimental conditions, *i.e.*, with minute iodide concentration, the nitrite formed in reaction (1) is oxidized by the excess of dinitrogen tetroxide to nitrate:[9]

$$N_2O_4 + 2NO_2^- \longrightarrow 2NO_3^- + 2NO \quad . . . . . (9)$$

This side reaction of the tetroxide has also been studied in a separate series of experiments. In a concentrated solution of alkali nitrite, dinitrogen tetroxide was caused to react by the same technique as for the iodide reaction. The gases evolved were absorbed by sodium hydroxide in which, besides nitrite, only an excess of nitric oxide was found. On increase of temperature, the concentration of the nitrite formed increases linearly while the quantity of nitric oxide diminishes.

[8] Dodé, *Bull. Soc. chim. France*, 1942, **9**, 449, 461.
[9] Seel *et al.*, ref. 2b.
[10] Szabó, Bartha, and Lakatos, *Acta Chim. Acad. Sci. Hung.*, in the press.
[11] Prahl and Raschig, *Z. angew. Chem.*, 1929, **42**, 253.

The possible reactions are as follows:

$$N_2O_4 + NO_2^- \longrightarrow NO_3^- + N_2O_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

$$NO_2 + NO_2^- \longrightarrow NO_3^- + NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9b)$$

$$NO_2 + NO \rightleftharpoons N_2O_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9c)$$

It must be assumed that, at a higher temperature, reaction (9b) prevails over (9a). However, the excess of nitric oxide can be considered as a result of reaction (9b) only if reaction between the nitrite and the nitrogen dioxide proceeds more rapidly than reaction (9c), but that is against all available evidence. In order to interpret the excess of nitric oxide, therefore, besides the above three processes, further reactions must be assumed which may lead to formation of nitric oxide. Disproportionation of nitrous acid, formed by hydrolysis of the tetroxide,[8] may be considered as such a process; *i.e.*, the rate of hydrolysis decreases with rising temperature, and, accordingly, the amount of nitric oxide resulting from disproportionation of the nitrous acid will do so, too. Hence, at a higher temperature, the excess of nitric oxide is smaller. Now it follows from the foregoing that, with nitrite ions present, hydrolysis of the tetroxide would be comparable with, or even more rapid than, the oxidation of nitrite. On the other hand, from this it necessarily follows also that, since reaction with the iodide proceeds by orders of magnitude more rapidly than the hydrolysis, the rate of reaction between the tetroxide and iodide ions is much higher than that between the tetroxide and nitrite.

On the basis of these experiments it is obvious that under the above conditions oxidation of the nitrite ions by the tetroxide cannot take place. In addition, however, a more rigid proof can be made based on the above experiments, namely, that, in reaction between the tetroxide and the iodide, the nitrate arises from a primary reaction and not through a secondary oxidation of the nitrite formed likewise in a primary step.

Obviously, all these reactions exert a greater or smaller influence on the ratio of nitrate to nitrite produced in the two principal reactions. Hence, to draw any concrete conclusion from this ratio on the influence of iodide-ion concentration, temperature, and pressure, all the side reactions must be eliminated or minimized. This was effected by suitable choice of experimental method and conditions. With the present technique the whole of the dinitrogen tetroxide undergoes reaction with the iodide ions, and the relatively good reproducibility of our results shows that side reactions have been suppressed. All runs were done in duplicate or triplicate and the reproducibility was within ±2%.

Results

Effect of Iodide-ion Concentration.—These experiments were carried out at 0°. The results (Table 1 and Fig. 2) show that, other conditions being unchanged, with rising iodide-ion concentration the quantity of the nitrate produced diminishes, and that of the nitrite increases.

TABLE 1. *Effect of iodide-ion concentration.* (Temp. 0°.)

KI (%)	N_2O_4 (g.) taken	N_2O_4 (%) converted into: NO_3^-	NO_2^-	NO	Total (%)*	KI (%)	N_2O_4 (g.) taken	N_2O_4 (%) converted into: NO_3^-	NO_2^-	NO	Total (%)*
10	0·2958	24·2	77·8	76·0	101·1	65	0·3240	62·7	37·2	36·6	99·6
	0·2731	22·8	77·0	75·6	99·1	85	0·3103	68·9	31·0	31·6	100·2
	0·2683	24·4	76·0	76·4	100·6		0·1818	68·8	30·6	31·4	99·8
25	0·2883	38·9	61·0	58·8	99·3	93	0·3116	69·3	30·2	30·0	99·4
	0·3418	41·0	60·2	60·6	101·4		0·1437	69·1	30·4	31·0	99·8
50	0·3121	56·4	43·6	44·8	100·6						
	0·2950	57·9	42·0	43·8	100·8						

* The totals are based on the nitrite plus the mean of the nitrate and nitric oxide.

Effect of Temperature (see Table 2).—These experiments were carried out in 10, 25, 35, and 50% solutions of potassium iodide, covering a temperature range 0—60°. With 10% potassium iodide, between 0° and 10°, the quantity of nitrate increases rapidly, at about 10° it passes through a maximum, then decreases gradually. The nitrite produced varies inversely, showing a minimum at 10° (Fig. 3, Curve *A*).

With 25% potassium iodide solution the results (Fig. 3, Curve *B*) are similar, but the maximum and the minimum both appear at about 15° and are somewhat lower than those obtained for the 10% solution.

With 35% potassium iodide (Fig. 3, Curve *C*), at first, the variation of nitrate is the same as it is subsequently after the maximum. From 10° upwards, the quantity of nitrate increases. The maximum, found at about 15°, is considerably lower than that mentioned above. The amounts of nitrite vary in the reverse direction throughout.

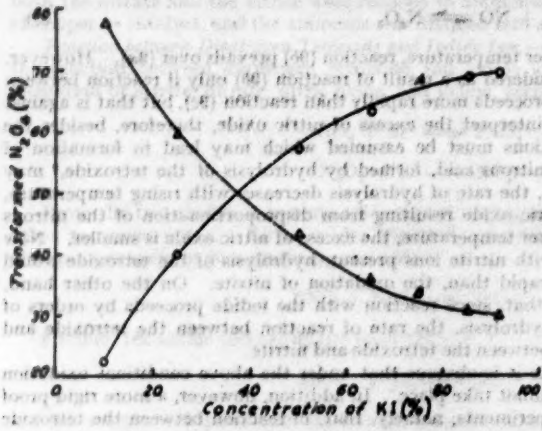


FIG. 2.

N_2O_4 (%) *converted into* (*A*) *nitrite and* (*B*) *nitrate.*

TABLE 2. *Effect of temperature.*

Temp.	N_2O_4 taken (g.)	N_2O_4 (%) converted into: NO_3^-	NO_2^-	NO	Total (%) *	Temp.	N_2O_4 taken (g.)	N_2O_4 (%) converted into: NO_3^-	NO_2^-	NO	Total (%) *
					(*a*) 10% KI Solution.						
0°	0·2958	24·2	77·8	76·0	101·1	20°	0·2943	30·0	70·8	70·4	100·6
	0·2731	22·8	77·0	75·6	99·1		0·3340	29·2	70·0	70·4	99·4
	0·2663	24·4	76·0	76·4	100·6	40	0·2858	43·2	56·4	55·6	99·2
5	0·3181	21·2	78·8	79·6	100·4		0·3216	44·2	56·0	57·2	100·8
	0·3347	21·0	79·6	79·8	100·7	60	0·3096	52·2	48·0	49·2	100·8
10	0·3446	17·1	83·8	83·2	100·6		0·3323	51·7	48·6	48·4	100·2
	0·3147	17·9	83·0	82·8	100·8						
15	0·2374	25·3	75·0	72·6	99·4						
	0·2864	25·6	75·6	74·2	100·6						
					(*b*) 25% KI Solution.						
0	0·7653	34·8	65·6	66·0	100·9	20	0·7692	33·1	67·0	67·8	100·5
	0·7664	35·2	64·0	65·4	99·9		0·7987	33·6	66·4	67·6	100·6
5	0·8343	35·9	63·8	62·8	99·2	40	0·7560	45·6	54·4	53·0	99·3
	0·8002	34·7	63·2	65·0	98·8		0·8361	46·5	55·4	54·0	101·2
10	0·7790	35·4	64·0	64·4	99·6	60	0·7709	55·0	45·4	45·6	100·5
	0·8158	34·5	65·2	65·4	99·8		0·7256	55·5	44·8	44·0	99·9
15	0·8121	29·8	70·2	71·4	100·6						
	0·8348	29·0	69·6	70·4	99·0						
					(*c*) 35% KI Solution.						
0	0·7380	42·0	58·4	59·4	100·9	15	0·6094	49·9	50·6	51·0	100·7
5	0·6298	46·4	53·2	54·6	100·3	20	0·6741	51·6	48·2	47·6	99·5
10	0·6248	52·4	47·6	47·0	99·7	25	0·7106	55·9	43·0	44·8	99·8
					(*d*) 50% KI Solution.						
0	0·9934	47·4	52·4	54·4	100·8	25	1·0283	59·5	40·0	39·6	99·3
	1·0245	46·2	53·2	55·8	100·7		0·9828	60·1	39·4	40·8	100·2
10	0·9352	50·7	49·2	49·8	100·2	40	0·9350	67·0	33·2	34·2	100·7
	0·9757	50·6	49·4	48·2	99·4		0·8766	68·9	31·4	31·8	100·5
15	0·9206	53·0	47·2	45·8	99·5	60	0·9213	72·5	27·6	25·8	99·2
	0·9616	53·7	46·2	45·6	99·6		0·9042	72·7	27·2	26·8	99·7
20	1·0357	57·2	42·6	43·2	100·1						
	0·9416	57·9	42·0	41·8	99·8						

* See footnote to Table 1.

The results with 50% potassium iodide solution are quite different (Fig. 3, Curve *D*). With rising temperature, the percentage of dinitrogen tetroxide converted into nitrite increases uniformly, while that of the nitrate diminishes, and no maximum (or minimum) is found.

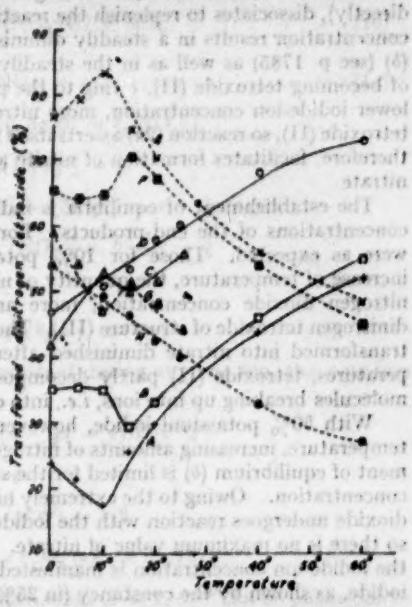


FIG. 3. *Transformation products of N_2O_4 in KI solution.*

Concn. (%) of KI soln.	10	25	35	50
Nitrite, curve	*A*	*B*	*C*	*D*
Nitrate, curve	*E*	*F*	*G*	*H*

Effect of Pressure.—Some experiments were carried out at a pressure corresponding to the vapour tension of the potassium iodide solution: the reaction changed in type, the nitrite becoming the principal product (see Table 3).

TABLE 3. *Effect of pressure.* (*Experiments in* 25% KI *solution*; *temp.* 0°.)

	N_2O_4 (%) converted into:			Total		N_2O_4 (%) converted into:			Total
Pressure	NO_3^-	NO_2^-	NO	(%)	Pressure	NO_3^-	NO_2^-	NO	(%)
1 Atm.	34·8	65·6	66·8	100·9	V. p. of KI soln.	89·7	10·2	10·2	99·9
.....	35·2	64·0	65·7	99·9	.....	90·6	9·6	10·4	100·6

The experimental observation that, other conditions being unchanged, with increasing quantity of dinitrogen tetroxide, the amount of nitrate produced increases while that of the nitrite diminishes, may be attributed to the effect of pressure. With smaller concentrations of tetroxide the opposite course is observed. Accordingly, we have endeavoured to take nearly the same amount of tetroxide into reaction in each experimental run.

DISCUSSION

Equilibrium between Dinitrogen Tetroxide and Nitrogen Dioxide.—The experiments summarized above may be interpreted as follows.

It is only the nitrogen dioxide radicals, and the tetroxide (II), or rather the nitrosonium and nitrate ions split off from this molecule, that are involved in the reaction with the iodide ions. Reaction (1) (p. 1786) proceeds with the nitrogen dioxide radicals:

$$NO_2 + I^- \longrightarrow NO_2^- + \tfrac{1}{2}I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

Reaction (2) really involves nitrosonium ions:

$$NO^+ + I^- \longrightarrow NO + \tfrac{1}{2}I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

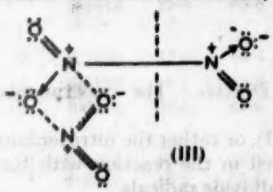
The effect of iodide-ion concentration therefore may be explained as follows. At first, both the nitrogen dioxide and the ions produced from the tetroxide (II) react with the iodide ions. Thereafter, the dinitrogen tetroxide of structure (I) (which cannot react directly), dissociates to replenish the reactive species. However, the increase of iodide-ion concentration results in a steadily diminishing possibility of establishment of equilibrium (*b*) (see p. 1785) as well as in the steadily decreasing amount of nitrogen dioxide capable of becoming tetroxide (II), owing to the preferential reaction with the iodide ions. With lower iodide-ion concentration, more nitrogen dioxide molecules can be transformed into tetroxide (II), so reaction (2*a*) asserts itself more intensely. A high iodide-ion concentration, therefore, facilitates formation of nitrite and, conversely, a low one favours production of nitrate.

The establishment of equilibria is indicated also by the effect of temperature on the concentrations of the end-products. For 10, 25, and 35% potassium iodide the results were as expected. Those for 10% potassium iodide were of particular interest: on increase of temperature, the quantity of nitrate at first increased rapidly; with increasing nitrogen dioxide concentration, more and more nitrogen dioxide was converted into dinitrogen tetroxide of structure (II). The percentage, however, of the dinitrogen tetroxide transformed into nitrate diminished after having reached a maximum; at higher temperatures, tetroxide (II) partly decomposed to nitrogen dioxide again, fewer and fewer molecules breaking up into ions, *i.e.*, into components involved in the " nitrate " reaction.

With 50% potassium iodide, however, the reaction proceeds differently. On rise of temperature, increasing amounts of nitrogen dioxide arise from structure (I), but establishment of equilibrium (*b*) is limited for the same reason as is given for the effect of iodide-ion concentration. Owing to the extremely high iodide-ion concentration, most of the nitrogen dioxide undergoes reaction with the iodide ions rather than conversion into tetroxide (II), so there is no maximum value of nitrate. To a smaller extent, the similar limiting role of the iodide-ion concentration is manifested in the experiments with 25 and 35% potassium iodide, as shown by the constancy (in 25% potassium iodide) or decrease (in 35% solution) of dinitrogen tetroxide converted into nitrate before it can reach its maximal value. Results obtained for 35% solution particularly illustrate the opposing effects of the two rival factors, (i) iodide-ion concentration and (ii) temperature, on the concentration of structure (II): the quantity of nitrate, after an initial decrease, increases again to reach a maximum, thus showing the superiority of (ii). For a 50% solution, there is no trace of such a maximum.

The results of pressure variation are also consistent. On decrease of pressure, the equilibrium N_2O_4 (I) $\rightleftharpoons$ $2NO_2$ $\rightleftharpoons$ N_2O_4 (II) undergoes a shift in favour of the nitrogen dioxide, so the concentration of the N_2O_4 (II) yielding the ions decreases, the " nitrate " reaction being inferior to the " nitrite " reaction.

Mechanism of Reaction: Kinetic Considerations.—It is only the nitrogen dioxide radicals and the tetroxide (II), or rather the nitrosonium and nitrate ions split off from the latter, that are involved in the reaction. The velocity of the whole transformation is determined by the following two reactions of the nitrogen dioxide: (i) in one a portion reacts with the iodide ions, (ii) in the other it is converted into tetroxide (II) to react further, after dissociating into ions.



(III)

The data now recorded are consistent with the consideration that the nitrogen dioxide radicals thermally dissociated from the tetroxide react, not with one another, but with an undissociated tetroxide to form the intermediate (III) by what may be regarded as bimolecular gas reaction (10). Owing to the fact that neither the tetroxide (I) nor the nitrogen dioxide * reacts with water, to a first approximation water may be considered as an indifferent medium but, since the reaction is between polarized systems, the action of water may be merely one of physical catalysis. The

* According to Denbigh and Prince's experiments,[24] the hydrolysis of tetroxide is slower at 40° than at 25°. This fact, as well as the authors' studies on the hydrolysis of tetroxide, suggest that the nitrogen dioxide fails to undergo hydrolysis.

decomposition of the intermediate (III) yields the tetroxide (II), as shown. On the basis of this consideration, therefore, the mechanism of the two reactions of nitrogen dioxide is as follows:

$$NO_2 + N_2O_4 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ONO_2{\cdot}NO + NO_2 \quad . \quad . \quad . \quad . \quad (10)$$

$$NO_2 + I^- \xrightarrow{k_2} NO_2^- + \tfrac{1}{2}I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

Whence $dy/dt = k_1[N_2O_4][NO_2]$ and $dx/dt = k_2[NO_2][I^-]$

where $[NO_2^-] = y$ and $[NO_3^-] = x$

Putting $[N_2O_4] = [N_2O_4]_0 - \frac{1}{2}[NO_2^-] - [NO_3^-] = a - \frac{1}{2}x - y$

and $[I^-] = [I^-]_0 - [NO_2^-] - [NO_3^-] = b - x - y$

we have, on division of dy/dt by dx/dt:

$$dy/dx = k_1(a - \tfrac{1}{2}x - y)/k_2(b - x - y)$$

As the iodide-ion concentration is virtually constant during any one run, this equation can be reduced to:

$$dy/dx = k_1[N_2O_4]/k_2[I^-] = k_1(a - \tfrac{1}{2}x - y)/k_2[I^-]_0$$

Solution of this equation, with $y_{x=0} = 0$, gives

$$y = (a + 1/2A)(1 - e^{-Ax}) - x/2$$

where $A = k_1/k_2b = \kappa/b$ and $\kappa = k_1/k_2$ (*i.e.*, $\kappa = Ab$)

If the initial iodide-ion concentration is high, then, since $A \ll 1$, e^{-Ax} can be put equal to $1 - Ax$, giving $y \simeq aAx$, whence $\kappa = by/ax$. The κ values thus calculated are summarized in col. 4 of Table 4, which also gives the values from Table 1 in terms of molar concentrations.

TABLE 4.

Concns. (10^{-4} moles/l.)			$\frac{by}{ax} = \kappa$	$\frac{by}{x}$	$\frac{x}{y}$	$[I^-] = b$ (moles/l.)
$N_2O_4 = a$	$NO_2^- = x$	$NO_3^- = y$				
3·215	1·556	2·502	301·3	0·969	0·622	0·402
2·068	1·354	2·286	342·6	1·017	0·592	
2·916	1·424	2·216	321·5	0·937	0·642	
3·133	2·438	1·912	377·0	1·181	1·275	1·506
3·715	3·046	2·236	297·6	1·105	1·362	
3·392	3·826	1·478	343·0	1·163	2·589	3·012
3·206	3·712	1·346	340·6	1·092	2·758	
3·521	4·416	1·314	330·9	1·165	3·361	3·915
1·976	2·738	0·600	567·8	1·122	4·437	5·120
3·372	4·666	1·030	335·2	1·130	4·498	
3·386	4·668	1·052	372·9	1·262	4·563	5·602
1·562	2·150	0·478	797·3	1·245	4·530	

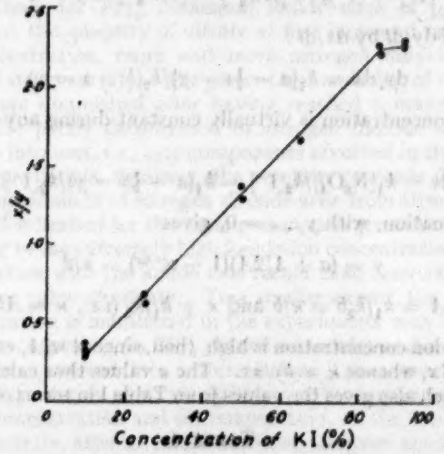
The values of by/ax are nearly constant if the quantity of tetroxide a is nearly the same. It follows from the experimental method that, because of the large excess of iodide ions, the concentration of tetroxide is independent of the quantity of N_2O_4 used, for more tetroxide reacts in a larger volume. Therefore, the tetroxide concentration may be regarded as being constant and can be introduced into κ. So the values k_1/k_2 are constant. On the basis of this consideration, therefore, the quotient x/y should be a linear function of the iodide ion-concentration, and this is proved by the results (see Fig. 4; for break in the curve, see below).

No conclusion could be drawn as to the dependence of the reaction upon temperature. Values of log κ plotted against $1/T$ did not give a straight line. This fact suggests that κ

represents, not only the quotient k_1/k_2, but also a term depending on the rate constants of other processes. Since, if the dioxide–tetroxide (II) transformation controlled the rate, the log $\kappa - 1/T$ should be linear, it is clear that another process takes part in the measured reaction velocity. This divergence may be interpreted by the assumption that, during the reaction, not an equilibrium but a stationary state is involved, so that the rate of dioxide–tetroxide (II) transformation as well as that of the dioxide–iodide reaction is greater than, or at least equal to, the tetroxide–dioxide dissociation rate. This means that the activation energy of the processes consuming dioxide cannot be larger than 11 kcal., *i.e.*, the energy of activation of the reaction $N_2O_4 \longrightarrow 2NO_2$.[12]

By assuming this stationary state, the results can be reinterpreted. Increase of temperature gives rise to an increase in dioxide concentration, and, therefore, also the reaction $NO_2 + O_2N{\cdot}NO_2 \longrightarrow ONO_2{\cdot}NO + NO_2$ yields more tetroxide (II) and the amount of

FIG. 4.



nitrate increases. Above a certain temperature, however, the nitrogen dioxide–iodide ion reaction becomes faster than the rate of formation of tetroxide (II). Thereafter the quantity of nitrate decreases steadily.

The reaction between tetroxide (II) and iodide ions was assumed to be very rapid, being faster than that between dioxide and iodide ions. A number of analogous reactions, *e.g.*, between potassium iodide and chlorine [13] or chlorine dioxide,[14] as well as the fact that these processes do not take place with perfectly dry potassium iodide, indicate that the electron transfer can only take place after the polarization of the electron system of the dioxide molecule. On the other hand, the reaction between the Longuet-Higgins structure and the iodide ion may be regarded as a reaction between an ion and a quasi-ion and so is extremely rapid. This assumption is supported by the consistency of calculations based upon it. Nevertheless, these kinetic considerations and results confirm the fact that the Longuet-Higgins formula cannot represent the total amount of the tetroxide, for if this were the case one would have obtained much more larger quantities of nitrate, increasing with increasing iodide concentration.

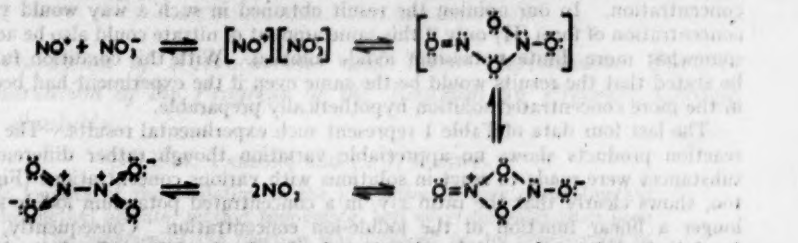
Structure of Dinitrogen Tetroxide (II).—On the basis of the various reactions of dinitrogen tetroxide, as already mentioned, it became necessary to assume, in addition to the known tetroxide structure (I), the existence of a structure which would explain the almost invariable formation of nitrate. This structure is the Longuet-Higgins formula, while the nitrosonium nitrate, as proposed *inter alia* by Seel *et al.*,[20] must be regarded as an

[12] Carrington and Davidson, *J. Phys. Chem.*, 1953, **57**, 418.
[13] Parsons, *J. Amer. Chem. Soc.*, 1925, **47**, 1817.
[14] Szabó, Beck, and Bergh, unpublished.

intermediate stage in the reactions. Tetroxide (I), together with the dioxide formed in the thermal dissociation, turns into the structure suggested by Longuet-Higgins to produce, first, with heteropolar or strongly polar partners and with temporary addition of electrons, the asymmetrical nitrosonium nitrate as critical complex, and thereafter, the nitrosonium and nitrate ions :

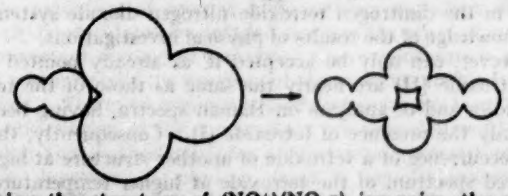
It appears from the mechanism that, in the Longuet-Higgins formula, the N^+ is able to compensate the electron affinity of oxygen, but after taking up the electron, because of the electron affinity of the three oxygen atoms, the N–O bond will break. Depending on the electronegativity of X, either $\cdot NO + \cdot X$ or NOX arises. If the reaction partners are of less polar character, then the fission of the Longuet-Higgins ring proceeds more symmetrically, in the NO_2^+ and the NO_3^- direction.[15]

In interpreting the dinitrogen tetroxide reactions, the intermediate existence of nitrosonium nitrate seems to be more probable in terms of the mechanism of the formation of dinitrogen tetroxide during the various reactions. In the reaction of nitrosonium salts with tetra-alkylammonium nitrates, quantitatively yielding dinitrogen tetroxide,[20] the nitrosonium ion should be joined up with two unpaired electrons while, simultaneously, the nitrate ion should be linked *via* its two oxygen atoms through 1–1 unpaired electrons to achieve the Longuet-Higgins formula directly from the ion-pairs. Now, neither the nitrosonium ion nor the nitrate ion has a single unpaired ion, and moreover, both of them are excited only with difficulty. Hence, the reaction proceeds as follows :



Such a course is rendered possible also by the fact that it corresponds to the principle of tending to reach a state of minimum energy. For during the passage from the heteropolar nitrosonium and nitrate ions towards the dinitrogen tetroxide, the dipole moment decreases steadily.

FIG. 5.



When establishing the structure of $(NO^+)(NO_3^-)$ ion-pairs, the nitrosonium nitrate formula must not be taken into account again because all the oxygen atoms of the nitrate ion are equivalent. Therefore, when a molecule is formed, the nitrogen atom of the nitrosonium ion must be joined with two oxygen atoms, so as to give a state of minimum energy (Fig. 5). From this bonding the Longuet-Higgins structure arises through a simple electron rearrangement. In this structure the oxygen atoms possess two π bonds, making an angle of 90° each, while the nitrogen atoms have two σ bonds of 120° each, so the ring

[15] See, *e.g.*, Levy and Scaife, *ref. 2f.*

exhibits a stress of (420°—360°)/4 = 15° for each angle, which is likewise in accordance with the properties of the molecule.

Concentration of the Dinitrogen Tetroxide (II).—For establishment of the structure of tetroxide (II), its concentration, too, may play an important part. Leaving aside, for a moment, the foregoing consideration, a very slight concentration of form (II) would permit the existence of the nitrosonium nitrate structure since its concentration would be so low that it could not be detected by physical methods. The presence of tetroxide (II) in a larger amount, however, excludes the nitrosonium nitrate structure, for its detection by physical methods would doubtless be feasible. On the other hand, if tetroxide (II) is identified with the Longuet-Higgins structure, then the experimental fact that physical methods refer only to the presence of tetroxide (I) as well as of nitrogen dioxide, can be interpreted merely by the assumption of the close identity of the physical properties of the Longuet-Higgins structure with those of the tetroxide (I).[3] In consequence, detection of the latter was not feasible. This aspect, in turn, permits larger quantities of tetroxide (II) to be present in the tetroxide–dioxide system.

On the basis of the above considerations, it would be of great importance to determine experimentally the concentration of tetroxide (II). For this purpose the following assumption was made. With a sufficiently high concentration of the iodide ion, dinitrogen tetroxide would convert into nitrate and nitric oxide only as much of the tetroxide (II) as was present in the system at first, at the given pressure and temperature. In this case, therefore, the amount of tetroxide (II) consumed cannot be replaced, since, because of the high concentration of iodide ions, the whole of the nitrogen dioxide undergoes reaction with these.

In view of the above, in a reaction with potassium iodide saturated at a given temperature, the amount of nitrate, or nitric oxide, would directly give the tetroxide (II) concentration. In our opinion the result obtained in such a way would yield the right concentration of form (II) only if this same amount of nitrate could also be achieved with a somewhat more dilute potassium iodide solution. With this condition fulfilled, it may be stated that the results would be the same even if the experiment had been carried out in the more concentrated solution hypothetically preparable.

The last four data of Table 1 represent such experimental results. The percentage of reaction products shows no appreciable variation though rather different amounts of substances were made to react in solutions with various concentrations (Fig. 2). Fig. 4, too, shows clearly that the ratio x/y, in a concentrated potassium iodide solution, is no longer a linear function of the iodide-ion concentration. Consequently, in the most concentrated potassium iodide solutions, the nitrate can be formed only from the tetroxide (II), originally present as well, so the concentration of the nitrate represents also that of the tetroxide (II), which is, therefore, at 0°, about 31%.

The experimental results for the concentration of tetroxide (II), therefore, again indicate the presence of the Longuet-Higgins structure. Presence of about 31% of nitrosonium nitrate in the dinitrogen tetroxide–nitrogen dioxide system is inconceivable in the light of our knowledge of the results of physical investigations.

This aspect, however, can only be accepted if, as already pointed out, the physical properties of the tetroxide (II) are nearly the same as those of the tetroxide (I). The results of *X*-ray studies and of analyses on Raman spectra, having been obtained below −10°, can justify only the presence of tetroxide (I). Consequently, these investigations do not exclude the occurrence of a tetroxide of another structure at higher temperatures. However, the infrared spectrum of the tetroxide at higher temperatures (*e.g.*, at 20° [17]) could also be made consistent with a structure of ethylene type. The possibility of this co-ordination is, among others, supported also by the fact that the two frequencies, consequent upon Sutherland's calculations but unobserved by him, have since been found by Perkins and Wilson.[18] At any rate, a number of bands of medium, or weak, intensity were considered by Sutherland to be combination lines, though in fact they might be lines of another tetroxide structure.

[16] Seel, ref. 2*b*.
[17] Sutherland, ref. 1*a*.

The rather high concentration of the tetroxide (II) found in the present investigation requires reconsideration of the results of infrared spectra.

Comparison of N_2O_5, N_2O_4, and N_2O_3.—According to our results, the reactions and structure of dinitrogen tetroxide occupy a middle position between those of the pentoxide and the trioxide. The former has an ionic structure also in its solid phase. This was supported, *e.g.*, by the studies of Ingold *et al.* :[18] in the spectrum of pure N_2O_5 lines of nitronium and nitrate ions could be seen at −40°. Moreover, the presence of NO_2^+ ions was proved by spectral and *X*-ray evidence also.[19] On the other hand, a structural study of dinitrogen tetroxide indicated the absence of ions in the solid phase. The nitronium ion, beyond question, has a less polarizing effect than nitrosonium ion. In the dinitrogen trioxide, the nitrosonium ion, being more strongly polarized, forms a covalent bond with the more polarizable nitrite ion to such an extent that the reactivity of dinitrogen trioxide decreases; *e.g.*, nitric oxide evolved in the sodium metal–liquid tetroxide interaction, with the excess of tetroxide, produces dinitrogen trioxide remaining unaffected by the metal.[20] Alkali carbonates react with dinitrogen tetroxide to give alkali nitrate and nitric oxide, whereas with dinitrogen trioxide no reaction proceeds.[21]

Thanks are offered to Dr. P. Huhn for the mathematical discussion concerning the kinetic studies of the reactions.

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[18] Ingold, Millen, and Poole, *Nature*, 1946, **158**, 480; Millen, *J.*, 1950, 2609.
[19] Cox, Jeffrey, and Truter, *Nature*, 1948, **162**, 259; Grison, Eriks, and de Vries, *Acta Cryst.*, 1950, **3**, 290.
[20] Addison and Thompson, *Nature*, 1949, **163**, 369.
[21] Oswald, *Ann. Chim.*, 1914, **1**, 45; Addison and Lewis, *J.*, 1953, 1319.

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351. *The Oxidation of Hydrocarbons and Their Derivatives. Part I. The Observation of the Progress of the Reaction by Pressure Change and by Analysis.*

By B. I. PARSONS and C. J. DANBY.

The kinetics of the oxidation in the gas phase of four esters (methyl formate, methyl acetate, methyl propionate, and ethyl formate) have been studied. The progress of the reaction was followed (*a*) by observation of pressure change, (*b*) by analytical measurement (mass spectrometric) of the rates of consumption of ester and of oxygen and the rates of formation of major products. The results show that the pressure-change measurements give a close indication of the progress of the reaction over its whole course.

THE kinetics of the oxidation of gaseous hydrocarbons and their derivatives are very complex and can only be elucidated by detailed study of the effect of many variables. For this a rapid and convenient method of measuring the reaction rate is absolutely essential. Laborious methods which restrict the numbers of observations are likely to cause important facts to be overlooked. The most commonly used technique has been to follow the course of the reaction by observation of the concomitant pressure change (Δp). There is much indirect evidence that this method provides a substantially correct measure of the rate. The risk of error, however, is obvious from a simple example. The reaction $C_2H_6 + 2\frac{1}{2}O_2 = 2CO + 3H_2O$ is attended by a pressure change (Δp) equal to +1·5 times the initial ethane pressure. If the initial step were $C_2H_6 + O_2 = C_2H_5{\cdot}O_2H$ then the ratio for this would be −1. Since complex intermediates certainly do play an important rôle in the mechanism there is a real uncertainty.

In the present work analyses by mass spectrometer have been used to compare the pressure changes observed in the gas-phase oxidation of some esters with (*a*) the consumption of the ester and of oxygen, and (*b*) the formation of carbon monoxide and carbon dioxide.

Experimental

Reactions took place in a silica vessel of about 250 c.c. capacity maintained at the required temperature in a thermostatically-controlled electric furnace. The reaction vessel was connected to a capillary mercury manometer, to storage vessels for reagents, and to the usual system of high-vacuum pumps. Provision was made for the withdrawal of the contents of the reaction vessel for analysis.

Analyses were made with a Metropolitan-Vickers mass spectrometer Type M.S.2 by conventional techniques. The admission of gas samples containing large proportions of oxygen to the ionisation chamber of a mass spectrometer leads to the more or less rapid reversal of the effects of the " conditioning " of the filament (a process for which the usual butene pre-treatment was used) with consequent deterioration in instrument stability. At the same time the mass spectra develop considerable spurious and variable contributions to the peak at *m/e* 28. These must arise through reaction of the oxygen with carbonaceous deposits either on the filament or in the ionisation chamber. By increasing the butene pressure at which the pre-treatment was

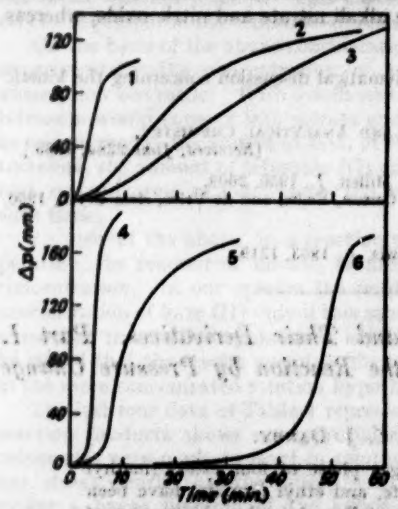


Fig. 1. *Δp–time curves for the oxidation of esters.*

1, Propyl formate. 4, Methyl butyrate.
2, Methyl formate. 5, Ethyl formate.
3, Methyl acetate. 6, Methyl propionate.

Temperature: Curve 1, 260°; curves 2—6, 380°.

carried out it was found possible to attain a state where these contributions to *m/e* 28 became reproducible and proportional to the oxygen pressure, so that reliable corrections could be made. The overall stability of the instrument then remained constant for sufficiently long to allow the analysis of five or six gas samples. The butene treatment then had to be repeated.

Water is a major product of the reaction and some of that formed may be lost by condensation. In the majority of experiments, therefore, all water vapour was removed with phosphoric anhydride from the samples before analysis. An accurately measured amount of helium was always added to the ester–oxygen mixture in the reaction vessel as a reference gas so that the partial pressures of reactants and products in the vessel at the moment of sampling could be calculated from the analytical results, irrespective of any removal of water vapour.

Experiments were made with methyl formate, methyl acetate, methyl propionate, and ethyl formate. The esters were dried (Na_2CO_3) and redistilled from phosphoric anhydride—a procedure which removes any unchanged alcohol or acid.[1] The accuracy of the analytical method was repeatedly checked by the analysis of synthetic mixtures containing known partial pressures of ester, oxygen, carbon monoxide, and carbon dioxide.

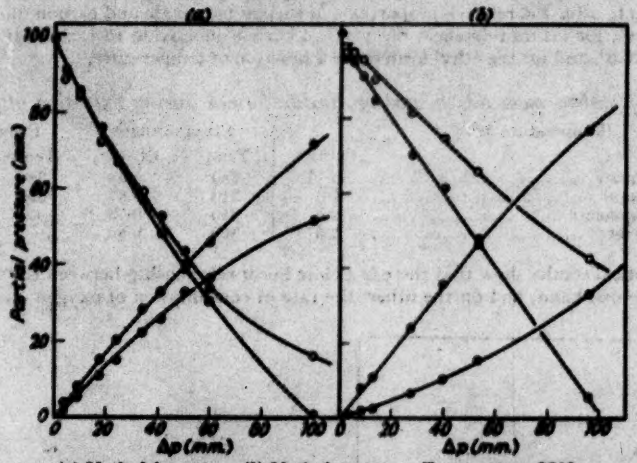
Results.—With each ester preliminary experiments were made to establish the form of the *Δp*–time curve. Series of successive experiments were then made in which gas samples for analysis were taken at representative points over the whole course of the reaction. As will appear in Part II,[2] ethyl formate differs from the other three esters in that its temperature–oxidation rate curve is of abnormal form, showing a maximum and a minimum. For this ester,

[1] Timmermans, " Physicochemical Constants of Pure Organic Compounds," Elsevier, 1950.
[2] Following paper.

therefore, analyses of products were made at a series of temperatures in the range 280—425°. With the other esters analyses were made at a single temperature.

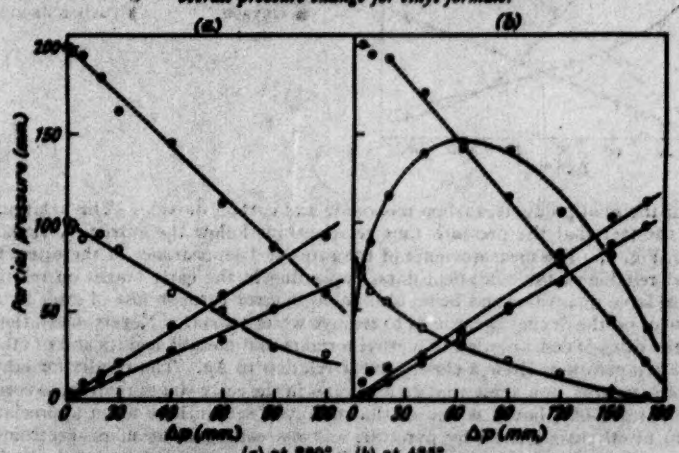
The mass-spectra of the products of oxidation, with the exception of those from methyl propionate, did not show any sign of residual peaks which could be attributed to complex

FIG. 2. *Rates of consumption of ester and oxygen and rates of formation of products as function of overall pressure change.*



(*a*) Methyl formate. (*b*) Methyl acetate. Temperature 380°.
○ Ester. ● Oxygen. ⊖ Carbon monoxide. ◑ Carbon dioxide.

FIG. 3. *Rates of consumption of ester and oxygen and rates of formation of products as function of overall pressure change for ethyl formate.*



(*a*) at 380°. (*b*) at 425°.
○ Ester. ● Oxygen. ⊖ Carbon monoxide. ◑ Carbon dioxide. ⊗ Ethylene (× 5).

intermediates. This was to be expected, as such compounds would be liable to condense on the walls of the sample vessel or be removed by the drying agent. The mass spectra of the reaction products from the oxidation of methyl propionate, however, showed small residual peaks at *m/e* 31 : this peak is prominent in the mass-spectra of a number of oxygen-containing organic compounds, particularly alcohols and ethers.

Fig. 1 shows the form of the Δp–time curves for the oxidation of the esters for which analytical measurements were made, together with those for methyl butyrate and propyl formate for comparison. Fig. 2 shows the rates of consumption of ester and of oxygen, and the rates of formation of carbon monoxide and carbon dioxide plotted against Δp for methyl formate and methyl acetate. Fig. 3 gives the corresponding results for methyl propionate and Fig. 4 those for ethyl formate at the two extremes of the temperature range.

The ratio of carbon monoxide to carbon dioxide varies from ester to ester, and one effect of temperature is to alter the relative proportions of carbon monoxide and carbon dioxide formed. The Table gives, for future reference, the ratio of carbon monoxide to carbon dioxide for the four esters at 380°, and for the ethyl formate as a function of temperature.

Ratio of carbon monoxide to carbon dioxide formed during oxidation of esters.

Temperature 380°		Ethyl formate		Ethyl formate	
Ester	CO/CO_2	Temp.	CO/CO_2	Temp.	CO/CO_2
Methyl formate	0·77	280°	0·58	380°	1·0
Ethyl formate	1·0	310	0·67	390	1·0
Methyl propionate	2·0	340	0·73	425	1·1
Methyl acetate	3·5	360	0·90		

The analytical results show that there is a close linear relationship between the total pressure change on the one hand, and on the other, the rate of consumption of oxygen and the rates of

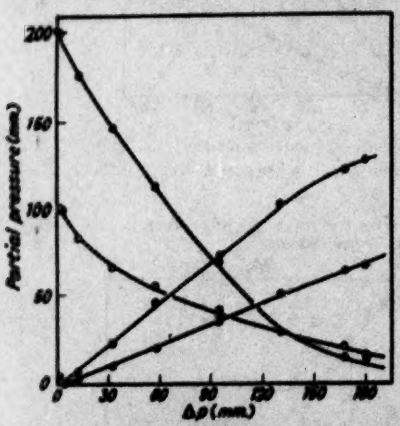


Fig. 4. *Rates of consumption of ester and oxygen and rates of formation of products as functions of overall pressure change for methyl propionate at 380°.*

○ Ester, ● Oxygen. ◒ Carbon monoxide. ◑ Carbon dioxide.

formation of the final products, carbon monoxide and carbon dioxide. This relationship holds in spite of the fact that the pressure–time relationships follow the extremely sigmoid courses portrayed in Fig. 1. The measurements of the rates of disappearance of the esters themselves are the least reliable of the analytical data, depending in the early stages on relatively small differences in large quantities and being also liable to error through loss of ester by absorption in tap-grease or on the drying agent used to remove water vapour. Nevertheless, the analytical results for the rates of consumption of methyl formate and methyl acetate and of ethyl formate at the lower temperatures show a closely linear relation to Δp. The results for ethyl formate at higher temperatures show somewhat greater rates in the early stages than those corresponding to exact proportionality, but it is known that pyrolysis sets in here to an appreciable extent. (The amount of ethylene formed by pyrolysis was also estimated by mass spectrometer and is shown in Fig. 3.) A similar divergence from a linear relation with Δp is also shown by the rate of consumption of methyl propionate. With this ester, however, the induction period is particularly long (Fig. 1) and, as mentioned above, signs of complex intermediates can be seen in the mass spectra, suggesting that particularly large amounts must have been formed.

Taken as a whole the results obtained show that, except under the most extreme conditions, the rate of pressure change is a reliable measure of the true rate of oxidation.

Physical Chemistry Laboratory, Oxford University. [*Received, October 24th*, 1955.]

352. *The Oxidation of Hydrocarbons and Their Derivatives. Part II.* Structural Effects in the Ester Series.*

By B. I. Parsons and Sir Cyril Hinshelwood.

A comparison is made, under standardised conditions, of the relative oxidation rates of a series of esters: methyl formate, methyl acetate, methyl butyrate, ethyl formate, methyl propionate, and propyl formate. Oxidation rates have been determined as a function of the concentrations of ester and of oxygen, and at a series of temperatures.

In one group the rate–temperature relation follows the Arrhenius law; in another the rate passes through a maximum and then a minimum as the temperature is raised.

The ease of oxidation is considered in relation to structure, and the results are found to be generally explicable in terms of the principles which have emerged from the study of other series of compounds.

The oxidation of hydrocarbons and their derivatives is profoundly influenced by structural changes. In particular, the substitution of methyl groups has a great stabilising influence, and the point of attack in the molecule which leads to the most rapid oxidation seems to be one as remote as possible from such groups. Chlorine atoms and alkoxy-groups (in ethers) facilitate oxidation and the replacement of a methylene by a carbonyl group retards it.[1]

Esters contain both carbonyl and alkoxy-groups, and in the aliphatic esters, R·CO·OR′, the number of methylene groups in either R or R′, or in both, can be varied. It is, therefore, of interest to see how far the structural principles mentioned above work out in this series.

The conditions of comparison are important. In the first place, oxidation rates are not simple functions of the reactant pressures, and these functions must first be examined. With the esters there is the usual relative insensitivity to oxygen pressure and the much more marked dependence on the ester pressure. In the second place, the rate may depend in a complex way upon temperature, rising, falling, and then rising again as the temperature increases. Where this abnormal dependence on temperature occurs it is convenient to distinguish the "low-temperature" region and the "high-temperature" region, there being good reason to believe that in the two the mechanisms of reaction are different.

The form of the rate–temperature curve, the structural effect, and the reaction mechanism are related in an important way. Peroxides are widely held to play an essential part in the mechanism, their fission into radicals giving rise, in the low-temperature region, to branching chains. The equations for the kinetics of such a branching-chain reaction show that a relatively small change in the ease of fission of the peroxide can produce a greatly magnified effect on the reaction rate. In this way, the exceptional sensitiveness of the oxidation to structural influences can be partly accounted for.[2] The abnormal temperature dependence is explained by the increasing loss of peroxide, as the temperature rises, in decompositions which do not help the chain branching (or as the result of the decomposition of precursors to the peroxide). Either process would lead to a fall in the rate of oxidation. The resumed rise at still higher temperatures is ascribed to the intervention of a new kind of mechanism, no longer directly associated with peroxide fission. If these considerations are valid, the great sensitiveness to structure evident in the low-temperature region should largely disappear in the high-temperature region.

Experimental

The reacting gases and vapours were placed in a heated silica vessel and the pressure changes accompanying oxidation were followed on a manometer. The validity of following the reaction

* Part I, preceding paper.

[1] (*a*) Cullis, Hinshelwood, and Mulcahy, *Proc. Roy. Soc.*, 1949, *A*, 198, 160; (*b*) Bardwell, *ibid.*, 1951, *A*, 207, 470; Hinshelwood, *Discuss. Faraday Soc.*, 1951, 10, 266; (*c*) Eastwood and Hinshelwood, *J.*, 1952, 733.

[2] Cullis, Hinshelwood, Mulcahy, and Partington, *Discuss. Faraday Soc.*, 1947, 2, 111.

by observation of pressure changes has been examined in Part I.[1] The reaction, in general, shows an induction period during which the rate rises to a maximum. Typical pressure–time curves for the six esters investigated have been given in Part I. The laws governing the

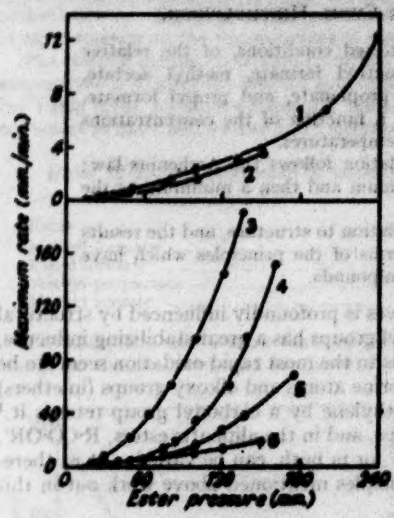
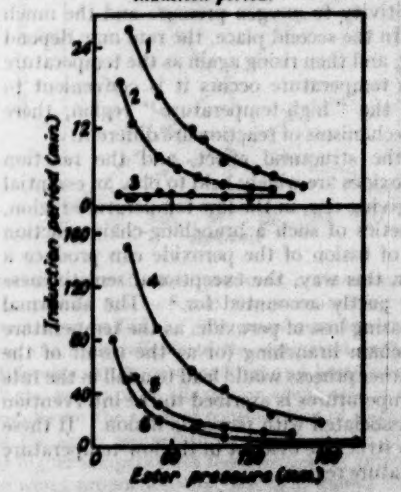


FIG. 1. *The effect of ester concentration on the maximum rate of oxidation.*

1. Methyl formate. 2. Methyl acetate.
3. Methyl butyrate. 4. Ethyl formate.
5. Methyl propionate. 6. Propyl formate.

Temperature: curves 1—5, 380°; curve 6, 260°. Oxygen pressure: 200 mm.

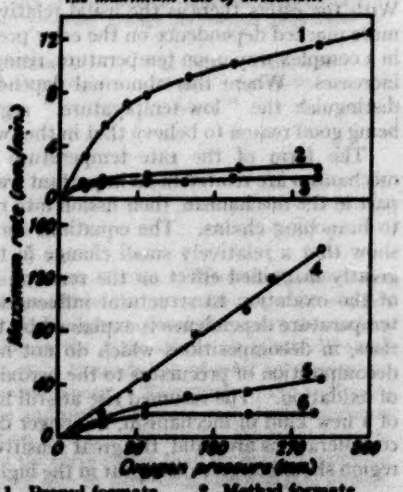
FIG. 2. *The effect of ester concentration on the induction period.*



1. Ethyl formate. 2. Methyl butyrate.
3. Propyl formate. 4. Methyl propionate.
5. Methyl acetate. 6. Methyl formate.

Temperature: curves 1, 2, 4, 5, 6, 380°; curve 3, 260°. Oxygen pressure: 200 mm.

FIG. 3. *The effect of oxygen concentration on the maximum rate of oxidation.*



1. Propyl formate. 2. Methyl formate.
3. Methyl acetate. 4. Methyl butyrate.
5. Ethyl formate. 6. Methyl propionate.

Temperature: curves 2 to 6, 380°; curve 1, 260°. Ester pressure: 100 mm.

influence of concentrations on the maximum rate and the induction period are not expressible by any simple formula, and for the present at least the dependence of each must be recorded separately. The important relations are shown in Figs. 1, 2, and 3.

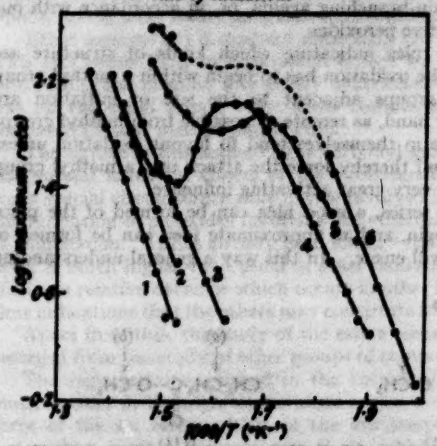
[1] Preceding paper.

The influence of initial concentrations on the maximum rate and induction period of the oxidation of the esters was very similar to that observed during the oxidation of the paraffins. In general, the rate is much more sensitive to the pressure of the organic vapour than to that of the oxygen. The induction period was equally dependent on the initial pressure of the combustible material. Except at very low oxygen pressures the induction period was independent of the initial oxygen concentration.

It is necessary to bear in mind the somewhat varying relations between rate and the pressures of oxygen or ester when comparisons between the different esters are made. The partial pressures chosen for most of the comparisons were 100 mm. of ester and 200 mm. of oxygen.

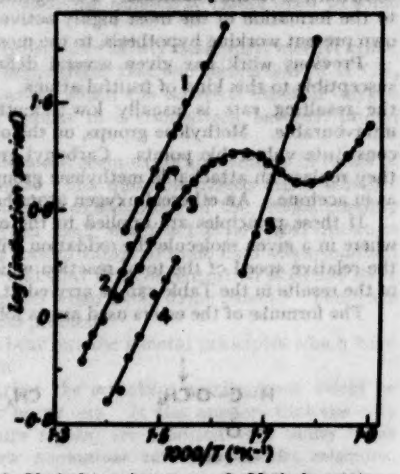
In order to construct a table of relative oxidation rates applicable at one given temperature, extrapolations are sometimes necessary, and for this purpose, as well as for the information the results give about the nature of the reaction mechanism, the temperature effect was determined in each example. The maximum rates are plotted in the conventional way in Fig. 4 as a function of temperature, and analogous results for the induction period are shown in Fig. 5. Since the

FIG. 4. *The effect of temperature on the maximum rate of oxidation.*



1. Methyl acetate.
2. Methyl formate.
3. Methyl propionate.
4. Ethyl formate.
5. Methyl butyrate.
6. Propyl formate.

FIG. 5. *The effect of temperature on the induction period.*



1. Methyl propionate.
2. Methyl acetate.
3. Ethyl formate.
4. Methyl formate.
5. Methyl butyrate.

rates for methyl formate and methyl acetate are nearly the same, the results selected for illustration in the case of methyl formate refer to 200 mm. initial ester pressure instead of the conventional 100 mm., this choice being made so that the curves for the two esters may be displaced relatively to one another and not interfere on the diagram.

It is clear from Fig. 4 that in the temperature range studied the esters fall into two very clearly defined groups: one in which the Arrhenius equation is followed, and the other in which the low- and high-temperature regions are distinguished, and separated by a region where the rate actually decreases with increasing temperature. Whether the characteristics of the second group would be shown by the first in another range of temperature cannot be said with certainty. What can be said, however, is that the factors responsible for the anomalous temperature effect in the esters of the second group are not operative in the other esters in any of the experiments carried out.

Structural Influences.—The relative values of the maximum rate of oxidation of the esters are shown in the Table. The experimental techniques used during the present study were very similar to those used in previous studies in this laboratory, and several approximate values of the corresponding rates of oxidation of normal hydrocarbons, ketones, and others are included in the list. Where the reactivities of the compound are very different the relative rates were

determined by the extrapolation of the log rate–$1/T$ plots until the temperature regions overlapped.

In an attempt to understand the influence of structure on the rate of oxidation it is necessary to consider also at which point in the molecule the initial attack occurs. The two problems are interconnected, since, although oxidation may begin in more than one place, it is only that

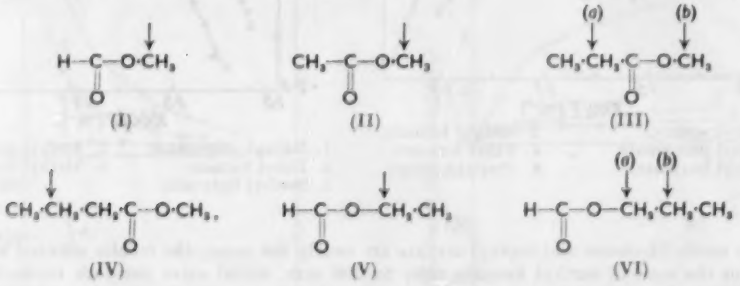
Compound	Maximum rate relative to methyl formate (low-temperature region)	(high temperature-region)	Compound	Maximum rate relative to methyl formate (low-temperature region)	(high temperature-region)
Methyl formate	1	1	*n*-Pentane	750	—
Methyl acetate	1	1	Pentan-2-one	750	—
Methyl propionate ...	6	6	Pentan-3-one	3500	—
Methyl butyrate ...	350	24	Dimethyl ether	20×10^3	—
Ethyl formate	350	3·6	Ethyl methyl ether	130×10^3	—
Propyl formate	2000	47			

attack which initiates a rapid and effective chain reaction which can lead to an important total contribution to the oxidation. The significant point of attack, therefore, is one which can lead to the formation of the most highly active chain-branching agents, or, in accordance with our own present working hypothesis, to the most active peroxides.

Previous work has given several definite rules indicating which kinds of structure are susceptible to this kind of fruitful attack. If the oxidation has to begin within a methyl group the resulting rate is usually low: methyl groups adjacent to the site of initiation are unfavourable. Methylene groups, on the other hand, as remote as possible from methyl groups constitute vulnerable points. Carbonyl groups in themselves tend to favour oxidation unless they replace an attackable methylene group, and thereby force the attack into a methyl group as in acetone. An ethereal oxygen atom has a very great activating influence.

If these principles are applied to the ester series, a good idea can be formed of the place where in a given molecule the oxidation will begin, and an approximate idea can be formed of the relative speed of the total reaction which will ensue. In this way a general understanding of the results in the Table can be arrived at.

The formulæ of the esters used are as follows:



(I) (II) (III) (IV) (V) (VI)

In view of the great activating influence of the ethereal oxygen it seems not unreasonable to assume that the effective attack on the esters (I) and (II) will be in the methyl group attached to this oxygen. But no methyl group is in itself a really advantageous point, so that esters (I) and (II) show relatively low rates. Methyl propionate (III) has a methylene group which could be attacked, but this is still adjacent to a methyl group. At which of the two points indicated by the arrows the attack by oxygen will lead to a more successful chain reaction is hard to say. If it is (*a*) this point is at least not in a methyl group itself, while if it is (*b*) a stabilising methyl group is one step further removed than in methyl acetate (II). Ester (III) thus shows a small but not important increase in rate. In esters (IV), (V), and (VI) the point of attack can move out of methyl groups, without becoming too remote from the ethereal oxygen. With these compounds the increase in rate, in the low-temperature region, is very marked. Since propyl formate (VI) has the greatest oxidation rate of the series it seems that the provision of a point of attack, (*a*) as remote as possible from the methyl group is the important factor.

Reference to the Table shows that in the high-temperature region the structural effects are considerably less pronounced than they are in the low-temperature region. It is also evident that with the esters (I), (II), and (III) there is one region only, and that the structural influence is small. The result is thus as though the single region of temperature dependence covered by the experiments has the characteristics of a " high-temperature " region. In these three esters it seems at least quite likely that the initial attack is in the methoxy-group itself. This may be the reason why anomalous temperature dependence, structure sensitivity, and also cool-flame production are all absent.

With esters (IV), (V), and (VI) attack is probably in a methylene group. In the low-temperature region the rate is enormously enhanced compared with that of the other esters. The usual effect of a lengthening of the carbon chain is evident in the comparison of esters (VI) and (V); propyl formate (VI) is considerably more easily oxidised than methyl butyrate (IV). The reason would seem to be that in the latter the propyl group is immediately adjacent to a carbonyl group, whereas in ester (VI) it is adjacent to the ethereal oxygen, which assists more powerfully.

On the whole, therefore, the ester series seems to offer a further general confirmation of the structural principles already illustrated by other groups of compounds.

The comparison of the esters with the ethers is of interest. For this purpose, a considerable degree of extrapolation is necessary, but this, while rendering numerical values open to some doubt, leaves none about the qualitative differences.

Ethyl formate (V) is oxidised something like 10^3 times more slowly than ethyl methyl ether. This fact seems hard to understand except by the supposition that the conversion of H CH_2 into H C:O has in some way partly neutralised the effect which the adjacent ethereal oxygen has on the ethyl group. The same consideration applies to a comparison between propyl formate (VI) and methyl propyl ether.

The nature of this action of the carbonyl group does not seem explicable simply in terms of the normal inductive effects of the substituent groups. The question indeed arises whether some special circumstance may not be involved in the great oxidisability of the ethers, possibly the formation of peroxides involving the ethereal oxygen itself, which act as powerful initiators of combustion. It has already been found[1c] that the concentration of some kind of peroxidised body is much higher than usual in ether oxidations, and that this concentration does not show the large relative decrease which occurs in other examples when a cool flame passes.[4] There are thus indications that the ethers may constitute a special problem.

Apart from this, the study of the esters seems to bear out the general principles which have emerged from the study of other groups of compounds.

The expectation expressed in the Introduction that the structure sensitiveness would be much smaller in the high-temperature region is fully borne out. It also appears that the only three of the six esters which, in the low-temperature region, are oxidised very many times faster than methyl formate are those which show anomalous rate–temperature relations. Thus the idea is further confirmed that the great influence of structure is upon something which as the temperature rises eventually ceases to be important, that is, according to the peroxide theory, the peroxide itself, or according to another theory a precursor of the peroxide.

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[*Received, October 24th*, 1955.]

[4] Bardwell and Hinshelwood, *Proc. Roy. Soc.*, 1951, *A*, **205**, 375.

353. *The Oxidation of Hydrocarbons and Their Derivatives. Part III.* The Rôle of Intermediates.*

By B. I. Parsons.

The products of oxidation by oxygen of methyl and ethyl formate and propane have been analysed chemically and polarographically. Formaldehyde, total aldehyde, and total acid analyses were made at six temperatures as the two regions of reactivity were traversed.

The polarograms of the oxidation mixtures showed two and sometimes three species present in the samples. The broad wave, characteristic of peroxide substances, was observed in all the analyses made. In the case of ethyl formate, as the temperature was increased, one species disappeared and was replaced by another. It was not possible to identify the two substances involved.

Changes during the actual passage of a cool flame could only be investigated with the propane–oxygen mixtures. Here a marked decrease in the concentration of peroxide occurred as the flame passed.

The more remarkable properties of hydrocarbon combustion include (*a*) the induction period followed by a rise in rate to a maximum, (*b*) the anomalous relation between rate and temperature, and (*c*) the occurrence in certain rather closely prescribed regions of concentration and temperature of cool flames, and sometimes of multiple bursts of cool flames.

These phenomena are closely interconnected. There is much to indicate that the active intermediates built up during the induction period are responsible for branching chains; and that the anomalous temperature effect is the result of alternative reactions of these intermediates or their precursors in side reactions, unfavourable to chain-branching. Severe changes in the concentrations of oxidation intermediates, principally peroxides, have been observed during the passage of a cool flame, and these same substances may well be responsible for the low-temperature explosion region.

The details of this general picture are, however, far from clear. Bardwell and Hinshelwood,[1] for example, found that during the passage of cool flames in butanone–oxygen mixtures there was a tremendous fall in the peroxide concentration. On the other hand, Eastwood and Hinshelwood [2] found that in the cool flames of ether the very much greater peroxide concentration suffered little proportional change (though some absolute decrease may have occurred).

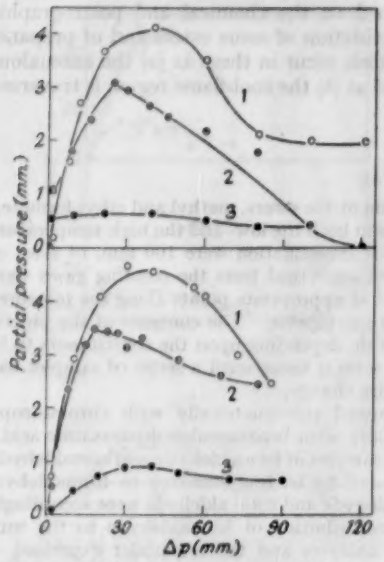
The large amount of discussion that has appeared in recent years on the probable nature and structure of the more likely chain-branching agents tends to obscure the considerable degree of general agreement that has been attained. Mechanisms of combustion have been proposed by Ubbelohde,[3] Walsh,[4] Norrish,[5] Knox and Norrish,[6] Cullis and Hinshelwood,[7] and others. Several are of the general form in which the initial attack by an oxygen molecule leads to an oxygenated hydrocarbon derivative capable of decomposition at normal combustion temperatures into two or more free radicals (not necessarily similar) and the propagation of a chain-branching mechanism.

That differences in detail have arisen is not surprising. A hydrocarbon (or derivative) can give rise in the course of its oxidation to peroxide, hydroperoxide, aldehyde, alcohol, acid, and oxides of carbon. All except the oxides may show pyrolysis, and any radical thereby produced can interact with oxygen. Which of the vast array of possible intermediates are those most closely connected with the general physical chemistry of the

* Part II, preceding paper.

[1] Bardwell and Hinshelwood, *Proc. Roy. Soc.*, 1951, *A*, **205**, 375.
[2] Eastwood and Hinshelwood, *J.*, 1952, 733.
[3] Ubbelohde, *Proc. Roy. Soc.*, 1935, *A*, **152**, 354.
[4] Walsh, *Trans. Faraday Soc.*, 1947, **43**, 297, 305.
[5] Norrish, XVI International Colloquium, Centre National de Recherche scientifique, 1948, p. 16.
[6] Knox and Norrish, *Proc. Roy. Soc.*, 1954, *A*, **221**, 151.
[7] Cullis and Hinshelwood, *Discuss. Faraday Soc.*, 1947, **2**, 117.

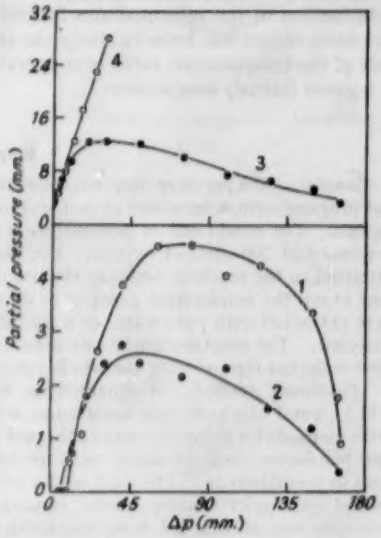
FIG. 1. *The formation of aldehyde and acid during the oxidation of ethyl formate.*



1. Formaldehyde. 2. Acetaldehyde. 3. Total acid.

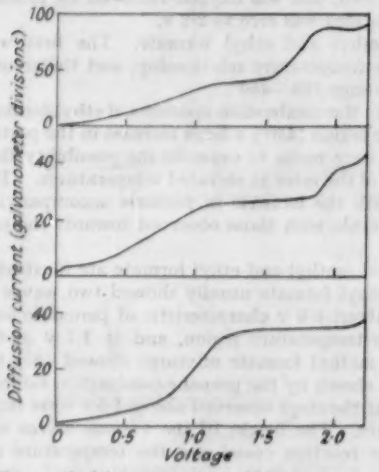
Top section of figure, 340°; bottom section, 280°.

FIG. 2. *The formation of aldehyde and acid during the oxidation and thermal decomposition of ethyl formate at 425°.*



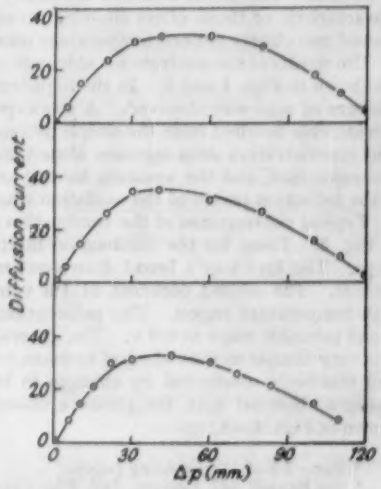
1. Formaldehyde.
2. Acetaldehyde.
3. Total acid (oxidation reaction).
4. Total acid (decomposition reaction).

FIG. 3. *Typical polarograms of the combustion mixtures of methyl and ethyl formate.*



Top: ethyl formate; Δp = 100 mm.; temperature = 425°.
Centre: ethyl formate; Δp = 20 mm.; temperature = 310°.
Bottom: methyl formate; Δp = 60 mm.; temperature = 390°.

FIG. 4. *The formation of peroxide (polarographic analyses) during the oxidation of methyl formate.*



Top: 450°. Centre: 415°. Bottom: 390°.

phenomena mentioned above is still largely to be decided, and experiments with new systems and as varied techniques as possible are therefore desirable.

In the present paper experiments are described on the chemical and polarographic examination of the intermediates formed in the oxidation of some esters and of propane. The main object has been to study the changes which occur in these as (*a*) the anomalous part of the temperature–rate curve is traversed and as (*b*) the cool-flame region is traversed at a given (initial) temperature.

Experimental

General.—The pressure–time curves of the oxidation of the esters, methyl and ethyl formate,[8] and propane were determined at various temperatures in both the low- and the high-temperature regions. The conditions of concentration selected for investigation were 100 mm. of ester or propane and 200 mm. of oxygen. For each series of analytical tests the reacting gases were admitted to the reaction vessel in the usual way, and at appropriate points along the pressure–time curve the combustion gases were shared with a gas pipette. The contents of the pipette were extracted with pure water or N/10-lithium chloride depending upon the constituents to be analysed. The reaction conditions were duplicated several times until a series of samples had been collected representing the whole range of pressure change.

Analytical Methods.—Formaldehyde was determined colorimetrically with chromotropic acid.[9] Total aldehyde was determined colorimetrically with benzenesulphohydroxamic acid.[10] Both methods for aldehyde were calibrated with pure samples of formaldehyde and acetaldehyde. The benzenesulphohydroxamic acid method was found to be less sensitive to formaldehyde than to acetaldehyde. The analyses for both formaldehyde and total aldehyde were accordingly carried out under exactly similar conditions; the contribution of formaldehyde to the total aldehyde was subtracted from the total aldehyde analyses and the remainder expressed as acetaldehyde. The results in each case were calculated back to the partial pressure of the component in the reaction vessel.

Total acid was determined by direct titration with 0·14N-sodium hydroxide at 0°, the indicator used being phenolphthalein. The solutions for titration were cooled in ice to prevent the rapid hydrolysis of the excess ester from obscuring the end-point.

For the polarographic analyses the method established by Shtern and Pollyak [11] was adopted. The contents of the gas pipette were extracted with N/10-lithium chloride. Two-ml. portions of the test solution were pipetted into the electrolytic cell, and the oxygen removed by passing hydrogen gas for 8·0 min. The voltage range investigated was zero to 2·2 v.

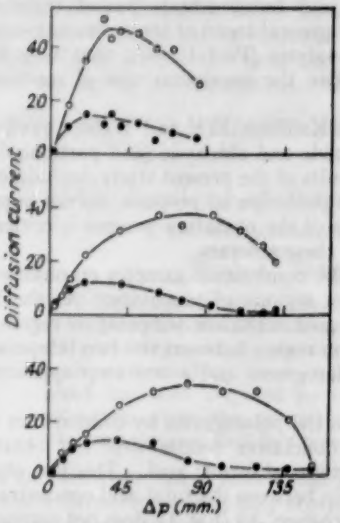
Results.—The esters selected for study were methyl and ethyl formate. The first was characteristic of those esters showing no anomalous temperature relationship, and the second showed two clearly defined temperature zones in the range 250—450°.

The results of the analyses for aldehyde and acid in the combustion mixtures of ethyl formate are shown in Figs. 1 and 2. In the high-temperature region (450°) a large increase in the partial pressure of acid was observed. A few experiments were made to examine the possibility that this increase resulted from the simple decomposition of the ester at elevated temperatures. The acid concentration does increase almost linearly with the increase in pressure accompanying decomposition, and the amounts formed are comparable with those observed towards the end of the induction period of the oxidation reaction.

Typical polarograms of the combustion samples of methyl and ethyl formate are illustrated in Fig. 3. Those for the combustion mixtures of ethyl formate usually showed two waves or steps. The first was a broad drawn-out wave at about 0·9 v characteristic of peroxidic substances. The second occurred at 1·9 v in the low-temperature region, and at 1·7 v in the high-temperature region. The polarograms of the methyl formate mixtures showed only the broad peroxide wave at 0·9 v. The general pattern shown by the propane combustion samples was very similar to that of ethyl formate, except that the steps observed above 1·5 v were small and relatively unaffected by changes in temperature. The height of the various waves and changes observed with the pressure changes in the reaction vessel and the temperature are shown in Figs. 4—8.

[8] Parts I and II, preceding papers.
[9] See Bricker and Johnson, *Ind. Eng. Chem. Anal.*, 1945, **17**, 400.
[10] See Damköhler and Eggerglüss, *Z. phys. Chem.*, 1942, *B*, **51**, 157.
[11] Shtern and Pollyak, *Acta Phys. Chem., U.R.S.S.*, 1939, **11**, 797.

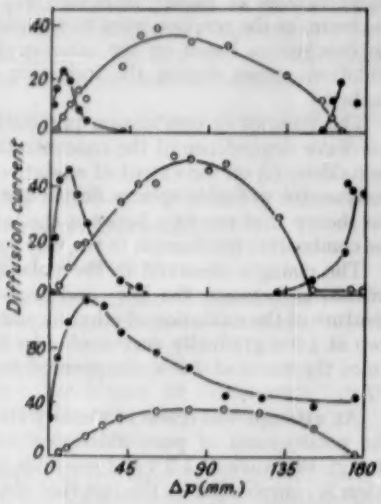
FIG. 5. *The variation in the height of the polarographic waves during the oxidation of ethyl formate.*



○ Wave at 0·9 v (characteristic of peroxide).
● Wave at 1·9 v (species unknown).

Top : 280°. Centre : 310°. Bottom : 340°.

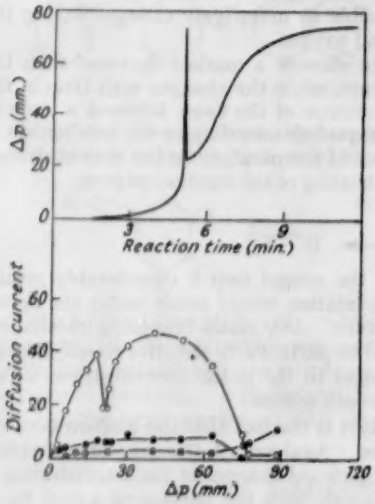
FIG. 6. *The variation in the height of the polarographic waves during the oxidation of ethyl formate.*



○ Wave at 0·9 v (characteristic of peroxide).
● Wave at 1·7 v (species unknown).

Top : 360°. Centre : 380°. Bottom : 425°.

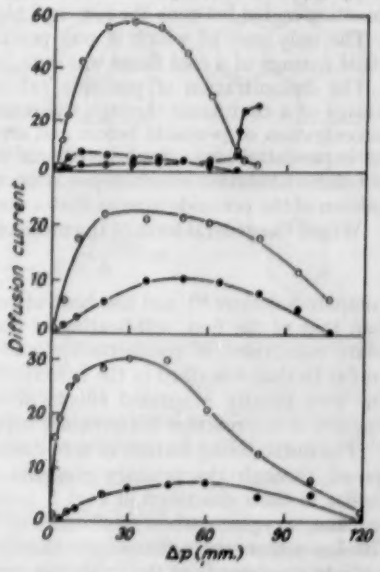
FIG. 7. *The variation in the height of the polarographic waves during the oxidation of propane at 300°.*



Top : typical pressure–time curve showing cool flame at Δp = 21 mm.
Bottom : Polarographic analyses :

○ Wave at 0·9 v (characteristic of peroxide).
⊖ Wave at 1·7 v (species unknown).
● Wave at 1·9 v (species unknown).

FIG. 8. *The variation in the height of the polarographic waves during the oxidation of propane.*



○ Wave at 0·9 v (characteristic of peroxide).
⊖ Wave at 1·7 v (species unknown).
● Wave at 1·9 v (species unknown).

Top : 280°. Centre : 370°. Bottom : 400°.

Discussion

In both the low- and the high-temperature regions of the oxidation of ethyl formate, the concentrations of higher aldehydes (C_2 upwards) and formaldehyde passed through a maximum as the reaction went to completion. The general trend of these results confirms the conclusions based on the mass-spectrometer analyses (Part I), *viz.*, that very little oxidation occurs during the induction period before the maximum rate of reaction is reached.

The theories of combustion proposed by Frank-Kamenetzki [12] and Walsh [4] predict a sine-wave dependence of the concentration of peroxide and aldehyde (and particularly of formaldehyde) on the extent of oxidation. The results of the present study, including the analyses for peroxide species during the cool-flame oxidation of propane, do not support the theory that reaction between the intermediates of the oxidation process is critical to the combustion mechanism in the way suggested by these schemes.

The changes observed in the polarograms of the combustion samples emphasise the differences between the low- and high-temperature regions of reactivity. As the temperature of the oxidation of ethyl formate was increased in the low-temperature region, the step at 1·9 v gradually decreased. In the transition region between the two temperature zones the wave at 1·9 v disappeared from the polarograms and a new step appeared at 1·7 v.

An attempt was made to identify the changes in the polarograms by comparisons with the polarograms of pure aldehydes and acids. Conclusive results were not obtained, though the wave at 1·7 v did resemble the polarograms of formic acid. This last observation is complicated by the fact that the relationship between the total acid concentration, as determined by direct titration, and the pressure change, Δp (Fig. 1), does not correspond to the changes observed in the height of the wave. There always exists the possibility of balancing reactions and separate laws governing the changes in the total acid and formic acid concentrations, but such changes would have to be quite complex. At the present stage in the investigation the best that can be inferred is that there is in fact the disappearance of one species and the appearance of a second during the traversing of the transition region between the low- and high-temperature regions of reactivity.

The only case in which it was practically feasible to investigate changes during the actual passage of a cool flame was with propane and oxygen.

The concentration of peroxide substances here showed a marked decrease with the passage of a cool flame through the reaction mixture, while the changes with time in the concentration of peroxide before and after the occurrence of the flame followed a more or less exponential law. Such behaviour would be expected according to the mechanism of cool-flame oxidation which depends upon the effect of temperature on the rate of decomposition of the peroxide intermediates and the self-heating of the reaction mixture.

Where the general form of the mechanism is

$$A + B \longrightarrow C \longrightarrow D + E$$

(compare Salnikov [13]) and the heat of reaction of the second step is considerably greater than that of the first, self-heating of the reaction mixture would result under the appropriate conditions of concentration and temperature. Any chain-branching mechanism similar to that described in the Introduction would be particularly sensitive to self-heating. The very greatly magnified effects of small changes in the initial concentrations of the reagents or the reaction temperature support some such scheme.

The outstanding feature of cool-flame combustion is the fact that the ignition does not spread through the primary reagents themselves. Analyses of the propane mixtures, similar to those described in Part I, indicate no significant changes in the concentration of propane, oxygen, carbon monoxide, or carbon dioxide with the passage of a cool flame. The low-temperature flames are clearly shown to be directly associated with the intermediate compounds of the oxidation process. Moreover, the position of the zone of cool-flame activity in the region of transition between the low- and high-temperature regions

[12] Frank-Kamenetzki, *Compt. rend. Acad. Sci., U.R.S.S.*, 1939, **25**, 671.
[13] Salnikov, *ibid.*, 1948, **60**, 405.

suggests that the substances decomposing explosively are the chain-branching agents of low-temperature oxidation.

These results, therefore, throw further light upon the general character of the phenomena in question. The proof, or disproof, of more detailed schemes lies undoubtedly in an analytical method for the isolation and examination of the inferred chain-branching substances and for the recognition of their modes of decomposition and oxidation.

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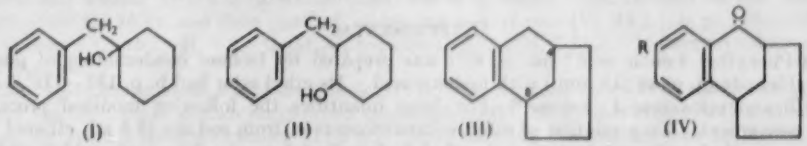
354. *Synthesis of Polycyclic Compounds. Part V.* The Cyclodehydration of 3-Benzylcyclohexanol.*

By J. C. BARDHAN and R. C. BANERJEE.

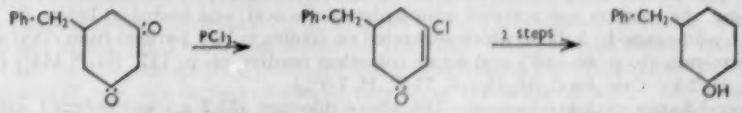
3-Benzyl*cyclo*hexanol, the preparation of which is described, on dehydration with phosphoric anhydride furnishes 4 : 8-*endo*methylenebenz*ocyclo*octene (III), yielding on oxidation with chromic acid the 3-ketone (IV). This has been synthesised by the cyclisation of 3-phenyl*cyclo*hexanecarboxylic acid, which has been prepared by two methods. The ketone, on Clemmensen reduction, gives the tricyclic hydrocarbon (III), and, consequently, the structure assigned to it by Cook and Hewett [1] is confirmed.

COOK and HEWETT [1] have shown that the dehydration of the alcohols (I) and (II) gives a tricyclic hydrocarbon which they represented as (III). This structure is in harmony with the resistance of the hydrocarbon to dehydrogenation, its conversion into phthalic acid, and its oxidation by chromic acid to the ketone (IV; R = H), which was further degraded to *cis*-hexahydro*iso*phthalic acid through the related phenol (IV; R = OH). However, the structures assigned to the hydrocarbon (III) and the ketone (IV; R = H) have not been confirmed by an alternative synthesis.



(I) (II) (III) (IV)

To extend this cyclisation, we have prepared 3-benzyl*cyclo*hexanol, by reactions shown in the annexed scheme. Curiously, on treatment with phosphoric anhydride this alcohol



gave the hydrocarbon (III); the yield was low but oxidation with chromic acid afforded the ketone (IV; R = H) which was readily characterised.

We have established the structure of the ketone (IV; R = H) by the following unequivocal synthesis. α-Phenylglutaric anhydride [2] was converted into the derived ethyl ester, and the latter condensed with ethyl oxalate in the presence of potassium ethoxide:

(V) $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}[CH_2]_2{\cdot}CO_2Et$ (VI)

(VII) $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}[CH_2]_2{\cdot}CO_2Et$

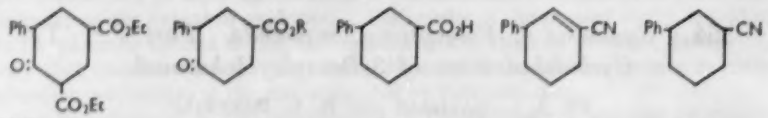
the resultant product on distillation gave a good yield of ethyl α-ethoxycarbonyl-α′-phenylglutarate (V). The sodio-derivative of this with ethyl β-chloropropionate gave ethyl

* Part IV, *J.*, 1956, 1346.

[1] Cook and Hewett, *J.*, 1936, 67.

[2] *Org. Synth.*, 1950, **30**, 817; Hornig and Finelli, *J. Amer. Chem. Soc.*, 1949, **71**, 3204.

$\gamma\gamma$-diethoxycarbonyl-α-phenylpimelate (VI), which on hydrolysis, elimination of carbon dioxide, and re-esterification afforded ethyl γ-ethoxycarbonyl-α-phenylpimelate (VII). Cyclisation with finely divided potassium then gave diethyl 4-oxo-5-phenyl*cyclo*hexane-1 : 3-dicarboxylate (VIII), hydrolysed by hydrochloric–acetic acid to the oily keto-acid (IX; R = H) which gave a crystalline semicarbazone. The corresponding ethyl ester on Clemmensen–Martin[3] reduction furnished 3-phenyl*cyclo*hexanecarboxylic acid (X) as a viscous liquid, apparently a mixture of *cis*- and *trans*-isomerides. However, a crystalline acid (X) was obtained by treatment of 3-phenyl*cyclo*hexanone with anhydrous hydrogen



(VIII) (IX) (X) (XI) (XII)

cyanide[4] followed by dehydration of the product with phosphoryl chloride and pyridine to the unsaturated nitrile (XI, and an isomeride); this was hydrogenated over palladised charcoal[5] to the saturated nitrile (XII) which on hydrolysis gave 3-phenyl*cyclo*hexanecarboxylic acid (X), m. p. 81°. From its method of formation the acid is tentatively regarded as having the *cis*-form.

Cyclisation of the crystalline acid (X) with polyphosphoric acid,[6] or by a Friedel–Crafts reaction, gave smoothly an excellent yield of the tricyclic ketone (IV; R = H) which had properties and derivatives in close agreement with those previously recorded.[1] Under similar conditions the impure liquid 3-phenyl*cyclo*hexanecarboxylic acid also afforded the ketone (IV; R = H) in about the same yield. Finally, the synthetic ketone was reduced by the Clemmensen procedure to the hydrocarbon (III), the structure of which is, therefore, fully established.

Experimental

4-Phenylbut-3-enoic acid[7] (m. p. 87°) was prepared by Döbner condensation of phenylacetaldehyde (b. p. 88°/18 mm.) with malonic acid. Its ethyl ester had b. p. 137—138°/5 mm.

*5-Benzyl*cyclo*hexane*-1 : 3-*dione*.[7b]—For large quantities the following modified procedure was convenient. To a solution of ethyl sodioacetoacetate [from sodium (6·5 g.), ethanol (107 ml.), and ethyl acetoacetate (40 ml.)], ethyl 4-phenylbut-3-enoate (55 g.) was added and the mixture heated on the water-bath for 10 hr. The sodio-derivative of the condensation product, which crystallised, was mixed with water (125 ml.), treated with potassium hydroxide (35 g.) in water (35 ml.), made up to 450 ml. with the addition of more water, and boiled for 15 min. On cooling, the solution was acidified with hydrochloric acid, and heated as before for 30 min. 5-Benzyl*cyclo*hexane-1 : 3-dione which separated on cooling is best purified from ethyl acetate–light petroleum (b. p. 60—80°) and forms colourless needles, m. p. 117° (lit.,[7b] 118°) (Found: C, 77·1; H, 7·1. Calc. for $C_{13}H_{14}O_2$: C, 77·2; H, 7·0%).

*5-Benzyl-3-chloro*cyclo*hex-2-enone*.—The above diketone (33·2 g.) was refluxed with phosphorus trichloride (7·3 ml.) and chloroform (82 ml.) for 4 hr. After removal of the chloroform, the residue was decomposed with cold water and extracted with ether. After being washed and dried in the usual way the ethereal solution was distilled. *5-Benzyl-3-chloro*cyclo*hex-2-enone* formed a colourless liquid (19·5 g.), b. p. 176—178°/5 mm. (Found: Cl, 16·4. $C_{13}H_{13}OCl$ requires Cl, 16·1%).

*3-Benzyl*cyclo*hexanone*.—The preceding compound (18·0 g) was hydrogenated in ethanol (30 ml.) in the presence of gum arabic (0·1 g.), water (5 ml.), and palladium chloride (0·1 g.). Absorption of hydrogen was complete in 1 hr. The *ketone* (14·5 g.), b. p. 142—144°/5 mm. (Found: C, 82·9; H, 8·6. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%), gave a *semicarbazone*,

[3] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[4] Wade and Panting, *J.*, 1898, **73**, 256.
[5] Hartung, *J. Amer. Chem. Soc.*, 1928, **50**, 3372.
[6] Birch, Jaeger, and Robinson, *J.*, 1945, 582; Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965; Birch and Smith, *J.*, 1951, 1885.
[7] (*a*) Vorlander, *Annalen*, 1906, **345**, 244; (*b*) Linstead and Williams, *J.*, 1926, 2741.

prisms (from ethanol), m. p. 168° (Found: C, 68·5; H, 7·9. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%).

3-*Benzyl*cyclo*hexanol*.—The foregoing ketone (5 g.) in absolute ethanol (50 ml.) was treated on a water-bath with sodium (5 g.) as rapidly as possible, the mixture being heated until no more sodium remained. The excess of ethanol was removed in steam and, after cooling, the residual liquid was extracted with ether, and the extract washed, dried (K_2CO_3), and distilled. 3-*Benzyl*cyclo*hexanol* formed a viscous oil (3·5 g.), b. p. 148—149°/ 5 mm. (Found: C, 82·3; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·4%).

4 : 8-endo*Methylenebenzo*cyclo*octene* (III).—The foregoing alcohol (3·8 g.) was heated with phosphoric anhydride (7·6 g.) at 145—150° for 1 hr. and then slowly distilled in a vacuum, giving an almost colourless oil (1·5 g.). This was dissolved in ether, washed with a little concentrated sulphuric acid, then with water, dried, and recovered by evaporation. On repeated distillation over sodium the hydrocarbon formed a colourless mobile liquid (1·1 g.), b. p. 100°/5 mm., $n_D^{20\cdot5}$ 1·5430 (lit.,[1] $n_D^{12\cdot8}$ 1·5523) (Found: C, 90·1; H, 9·1. Calc. for $C_{13}H_{16}$: C, 90·6; H, 9·4%). It was saturated towards the usual reagents. On oxidation with chromic acid in purified acetic acid it gave the ketone (IV), b. p. 129—132°/5 mm., whose semicarbazone had m. p. and mixed m. p. 222—223° (lit.,[1] 222—224°) (Found: N, 17·2. Calc. for $C_{14}H_{17}ON_3$: N, 17·3%).

Ethyl α-Phenylglutarate.—Ethyl α-cyano-α-phenylacetate (b. p. 135—138°/5 mm.), prepared by the action of sodium on a solution of benzyl cyanide and ethyl carbonate in dry ether, was converted into the anhydride (b. p. 192—195°/5 mm., m. p. 94—95°) by known methods.[2] The anhydride (21 g.) was refluxed with absolute ethanol (40 ml.), concentrated sulphuric acid (3 ml.), and benzene (42 ml.) for 5 hr. The *ethyl ester* was an oil (24 g.), b. p. 152—153°/5 mm. (Found: C, 68·4; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

Ethyl α-Ethoxycarbonyl-α'-phenylglutarate (V).—Ethyl oxalate (9·4 g.) was added to a suspension of potassium ethoxide in ether [prepared from powdered potassium (2·5 g.), calcium-dried ethanol (2·96 g.), and ether (70 ml.)]. The clear solution was cooled in ice and treated drop-wise with ethyl α-phenylglutarate (17·2 g.) in a little ether. The dark brown solution was kept at room temperature for 2 days, then diluted with ice water, the aqueous solution was separated and acidified with dilute sulphuric acid, and the oil was extracted with ether. The ethereal solution was washed with a little water, dried, and evaporated. The residual oil was heated at 180—190° for 10 hr. and then distilled, giving the *triethyl ester* (V) (15 g.), b. p. 183—185°/4 mm. (Found: C, 64·1; H, 7·3. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·1%). It gave no colour with ferric chloride.

Ethyl γγ-Diethoxycarbonyl-α-phenylpimelate (VI).—To a cooled solution of sodium (2 g.) in ethanol (36 ml.), ethyl α-ethoxycarbonyl-α'-phenylglutarate (30 g.) was added, followed, after cooling, by ethyl β-chloropropionate (12·3 g.). Next morning the mixture was heated on the water-bath for 6 hr. The excess of ethanol was removed, water was added to the residue, and the oil extracted with ether and fractionated. The *ester* (VI) formed a pale yellow liquid (12·2 g.), b. p. 210—212°/4 mm. (Found: C, 63·1; H, 7·2. $C_{25}H_{32}O_8$ requires C, 63·3; H, 7·3%).

Ethyl γ-Ethoxycarbonyl-α-phenylpimelate (VIII).—The preceding ester (72 g.) was refluxed for 1·5 hr. with potassium hydroxide (50 g.) in water (50 ml.) and ethanol (200 ml.). The crude acid, isolated in the usual way, was heated at 170—180° until no more carbon dioxide was evolved (3 hr.). The product (45 g.) was esterified by absolute ethanol (70 ml.) and concentrated sulphuric acid (7 ml.), in a current of ethanol vapour, at 110—115° for 6 hr. The *triethyl ester* (VII) formed an almost colourless liquid (42 g.), b. p. 192—194°/ 5 mm. (Found: C, 65·8; H, 7·6. $C_{20}H_{28}O_6$ requires C, 66·0; H, 7·7%).

Diethyl 4-*Oxo*-5-*phenyl*cyclo*hexane*-1 : 3-*dicarboxylate* (VIII).—The above tricarboxylic ester (18·2 g.) was added to a suspension of finely divided potassium (2·4 g.) in benzene (40 ml.), cooled in ice. As soon as the vigorous reaction was over, the mixture was heated on the water-bath until the last traces of potassium were dissolved. The product was worked up as usual, giving the *keto-ester* (9·5 g.), b. p. 205—206°/5 mm. (Found: C, 67·6; H, 6·9. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·9%). An ethanolic solution of the ester gave a violet colour with ferric chloride.

Ethyl 4-*Oxo*-5-*phenyl*cyclo*hexanecarboxylate* (IX; R = Et).—The preceding keto-ester (5·2 g.) was refluxed for 10 hr. with concentrated hydrochloric acid (10 ml.) and glacial acetic acid (20 ml.). The keto-acid (IX; R = H) (3 g.), isolated in the usual way, was an oil. Its *semicarbazone* formed colourless prisms (from ethanol; charcoal), m. p. 225° (decomp.) (Found: C, 61·4; H, 6·2. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·1%). The *ethyl ester* (IX; R = Et), prepared from the acid (14·4 g.) and ethanolic hydrogen chloride (48 ml.; 3%), was a

liquid (12·2 g.), b. p. 183—184°/5 mm. (Found: C, 73·1; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). A semicarbazone could not be obtained under the usual conditions.

Ethyl 3-*Phenylcyclohexanecarboxylate*.—The keto-ester (IX; R = Et) (10 g.) was refluxed for 30 hr. with amalgamated zinc (20 g.), concentrated hydrochloric acid (70 ml.), water (30 ml.), acetic acid (2 ml.), and toluene (40 ml.). The product (6 g.) obtained on evaporation of the combined toluene layer and ether-extracts of the aqueous layer was hydrolysed with 10% ethanolic potassium hydroxide in the usual way. The oily acid isolated as usual was converted into the *ethyl ester* (4·5 g.), b. p. 145—146°/5 mm. (Found: C, 77·3; H, 8·5. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). This on hydrolysis with alkali yielded the acid as an oil.

1-*Cyano*-3-*phenylcyclohexene* (XI). 3-Phenylcyclohexanone [6] (b. p. 138—139°/5 mm.) (5 g.) was added to hydrogen cyanide [4] (from potassium cyanide, 10 g.), and cooled to 0°. After the addition of a drop of potassium cyanide solution the mixture was kept at this temperature overnight; a drop of sulphuric acid was then added, and the excess of hydrogen cyanide removed at the water-pump. The crude product was heated with phosphoryl chloride (23 ml.), and dry pyridine (85 ml.) at 140—150° for 1 hr., then cooled, treated with ice, and poured into dilute hydrochloric acid, and the unsaturated nitrile was extracted with ether. The ethereal extract was washed with dilute sulphuric acid, then aqueous sodium hydroxide, and dried, and the solvent was removed. The residue gave the unsaturated *nitrile* (3·5 g.), b. p. 150—152°/5 mm., having a characteristic smell (Found: C, 85·5; H, 7·3. $C_{13}H_{13}N$ requires C, 85·2; H, 7·1%).

1-*Cyano*-3-*phenylcyclohexane* (XII).—The above-mentioned unsaturated nitrile (6 g.), ethanol (5 ml.), and palladised charcoal [5] (1 g.; 10%) were shaken in hydrogen until the calculated amount of hydrogen (830 ml.; 30°/760 mm.) was absorbed (1 hr.). The catalyst was filtered off, excess of ethanol removed, and the residual liquid distilled. The *nitrile* (5·7 g.) had b. p. 145—146°/5 mm. (Found: C, 84·1; H, 8·3. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1%).

3-*Phenylcyclohexanecarboxylic Acid* (X).—The foregoing nitrile (5 g.) was refluxed with potassium hydroxide (4 g.), water (4 ml.), and ethanol (15 ml.), until no more ammonia was evolved (40 hr.). The *acid* which separated on acidification was collected and formed needles, m. p. 81°, from dilute acetic acid (charcoal) (Found: C, 76·5; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

4 : 8-endo*Methylenebenzocyclooctene*-3-*one* (IV; R = H).—(*a*) The preceding acid (1 g.) was heated on the water-bath with phosphoric anhydride (6 g.) and phosphoric acid [6] (6 ml.; 85%) for 1·5 hr. After cooling, ice and water were added, the product was extracted with ether, the ethereal solution washed with a dilute solution of ammonia and with water and dried, and the solvent removed. The residual oil (0·7 g.) readily formed a semicarbazone, which separated in needles, m. p. 222—223° (lit.,[1] 222—224°) from ethanol (Found: C, 69·3; H, 7·3. Calc. for $C_{14}H_{17}ON_3$: C, 69·1; H, 7·0%). The pure ketone regenerated from the semicarbazone (4 g.), on distillation in an all-glass apparatus, formed a colourless oil (2·5 g.), b. p. 130°/5 mm., $d_4^{20\cdot5}$ 1·10659, $n_D^{20\cdot5}$ 1·5726, $[R_L]_D$ 55·35 (Calc., 54·24) (lit.,[1] $d_4^{19\cdot5}$ 1·11385, $n_D^{19\cdot5}$ 1·5770, $[R_L]_D$ 55·38) (Found: C, 83·6; H, 7·6. Calc. for $C_{13}H_{14}O$: C, 83·8; H, 7·6%). The oxime, by which the ketone can be readily characterised, crystallised from ethanol in needles, m. p. 122—123° (lit.,[1] 123—124°) (Found: C, 77·7; H, 7·4. Calc. for $C_{13}H_{15}ON$: C, 77·6; H, 7·5%). (*b*) The acid (X) (4·5 g.) was gently heated with thionyl chloride (3 ml.), excess of the reagent removed under reduced pressure, and the residue dissolved in carbon disulphide (20 ml.). The solution was cooled in ice, powdered anhydrous aluminium chloride (4 g.) was added all at once, and the mixture left overnight at room temperature. The product was decomposed with ice and dilute hydrochloric acid; the carbon disulphide solution yielded the ketone (2·5 g.), b. p. 129—130°/5 mm. which formed a semicarbazone, m. p. 222—223°, and an oxime, m. p. 122—123°, identical with those described above.

4 : 8-endo*Methylenebenzocyclooctene* (III).—The foregoing ketone (2·3 g.) was reduced with amalgamated zinc (10 g.), and hydrochloric acid (20 ml.) during 10 hr. The pure hydrocarbon, on distillation over sodium, formed a colourless liquid (1·2 g.), b. p. 99°/5 mm., $d_4^{20\cdot5}$ 1·0075, $n_D^{20\cdot5}$ 1·5535, $[R_L]_D$ 54·65 (Calc., 54·23) (lit.,[1] d_4^{14} 1·020, n_D^{14} 1·5580, $[R_L]_D$ 54·47) (Found: C, 90·5; H, 9·3%).

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[*Received, November 8th*, 1955.]

[6] Crossley and Renouf, *J.*, 1915, **107**, 608; Boyd, Clifford, and Probert, *ibid.*, 1920, **117**, 1382; France, Heilbron, and Hey, *ibid.*, 1939, **155**, 1288.

355. *Cyclic Sulphites derived from the Chloropropanediols.*

By P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson.

The products of the reaction between thionyl chloride and 2-chloropropane-1 : 3-diol include two crystalline products, identified as the geometric isomers of the cyclic 2-chlorotrimethylene sulphite. Infrared absorption spectra of these and of related compounds are discussed with reference to the conformational and configurational problems involved.

The reaction of thionyl chloride with 1 : 2- and with 1 : 3-diols is known to result in the formation, often in good yield, of cyclic sulphites, and a number of these have been described.[1,2] Geometrical isomerism dependent on the pyramidal arrangement of the groups attached to the sulphur atom should be possible in suitably substituted sulphites, by analogy with the similar geometrical isomerism observed in sulphoxides.[3] In the present work, the reaction between thionyl chloride and 2-chloropropane-1 : 3-diol has been studied. Fractional distillation of the product gave two isomeric sulphites, A, m. p. 42°, and B, m. p. 62°. Their infrared spectra have been compared with those of related compounds, including the cyclic sulphite of 5β-cholestane-3β : 5-diol. In this compound, the rather rigid steroid skeleton limits the conformational possibilities for the position of the S=O bond. From the comparisons, it is deduced that compounds A and B are the geometric isomers of 2-chlorotrimethylene sulphite. Their conformations and configurations are discussed below in terms of conformational analysis.[4,5]

Note added May 1st, 1956.—Szmant and Emerson[5a] reported the infrared stretching frequencies of the S=O bonds in some of the cyclic sulphites examined by us. Their values for ethylene sulphite (1220 cm.$^{-1}$) and propylene sulphite (1222 cm.$^{-1}$) agree fairly well with ours (1214 and 1215 cm.$^{-1}$ respectively). Their value for trimethylene sulphite (1220 cm.$^{-1}$) differs from ours; since they used a dilute solution in carbon tetrachloride, they possibly failed to resolve the two bands which we observed for this compound at 1190 cm.$^{-1}$ and 1234 cm.$^{-1}$. From the regularity of its occurrence in 1 : 3-sulphites, we regard the former band as that of the S=O stretching vibration.

Experimental

2-Chloropropane-1 : 3-diol was prepared by the method of Glattfield *et al.*[6] A monochlorohydrin mixture (300 g.; prepared from allyl alcohol and chlorine in the presence of aqueous sodium carbonate) was treated several times with acetone in the presence of sulphuric acid and sodium sulphate. Each time, the *iso*propylidene derivative of 3-chloropropane-1 : 2-diol was separated from the residual monochlorohydrin mixture, which in this way was gradually enriched in 2-chloropropane-1 : 3-diol. Finally, there was obtained a product (60 g.), b. p. 96—98°/3 mm., n_D^{25} 1·4818. Kinetic analysis[7] of this showed that less than 10% of the isomeric diol was present.

3-Chloropropane-1 : 2-diol was recovered from its *iso*propylidene derivative, obtained as a by-product in the above preparation. It had b. p. 96—98°/3 mm., n_D^{25} 1·4790, and a 0·054N-solution reacted with 0·054N-sodium hydroxide in water at 25° with k_2 = 10·8 l. mole^{-1} min.$^{-1}$.

Reaction of Thionyl Chloride with 2-Chloropropane-1 : 3-diol.—2-Chloropropane-1 : 3-diol (20 g.) was refluxed for 12 hr. with thionyl chloride (13·4 ml.) and ether (100 ml.). The product was fractionated, giving the following materials: (i) 13 g., b. p. 67—73°/12 mm.; this solidified on cooling, and recrystallisation from water gave trans(?)-*2-chlorotrimethylene sulphite* as needles (A), m. p. 42° (Found: C, 22·7; H, 3·0; Cl, 22·3; S, 20·2. $C_3H_5O_3ClS$ requires C, 23·0; H, 3·2; Cl, 22·7; S, 20·5%). (ii) 7 g., b. p. 73—84°/12 mm., solidifying partly on cooling.

[1] Carlson and Cretcher, *J. Amer. Chem. Soc.*, 1947, **69**, 1952.
[2] Majima and Simanuki, *Proc. Imp. Acad. (Tokyo)*, 1926, **2**, 545.
[3] Bell and Bennett, *J.*, 1927, 1798; 1929, 15.
[4] Barton, *J.*, 1953, 1027.
[5] Klyne, "Progress in Stereochemistry," Butterworths, London, 1954, p. 36.
[6] Glattfield, Seavell, Spieth, and Hutton, *J. Amer. Chem. Soc.*, 1931, **53**, 3169.
[7] Smith, *Z. phys. Chem.*, 1918, **92**, 717.

(iii) 3 g., b. p. 96°/12 mm., solidifying on cooling. Recrystallisation from water gave cis(?)-2-*chlorotrimethylene sulphite* as plates (B), m. p. 62° (Found: C, 23·0; H, 3·2; Cl, 23·1; S, 20·4%). The materials A and B were not dimorphic forms of the same substance, since they had different b. p.s, and a mixture of the two was liquid at room temperature.

Reaction of Thionyl Chloride with 3-Chloropropane-1 : 2-diol.—3-Chloropropane-1 : 2-diol (10 g.) was refluxed for 12 hr. with thionyl chloride (6·7 ml.), toluene (50 ml.), and ether (50 ml.). Fractional distillation gave *3-chloropropylene sulphite* (9·5 g.), b. p. 95°/12 mm., 210°/760 mm., n_D^{20} 1·4808 (Found: C, 23·4; H, 3·6; Cl, 19·7; S, 22·5%).

Reaction of thionyl chloride with this diol in the presence of pyridine gave mixtures containing also dichlorohydrins and trichloropropane.

Cyclic Sulphite of 5β-Cholestane-3β : 5-diol.—This was prepared by the method used for anhydrostrophanthidin 3 : 5-sulphite by Plattner, Segre, and Ernst.[8] The diol (135 mg., double m. p. 141—142°, 150—152°; Plattner, Heusser, and Kulkarni [9] report m. p. 149°) was dissolved in dry chloroform (15 ml.), and *ca.* 5 ml. of chloroform were distilled off. The solution

Infrared absorption bands (cm.$^{-1}$) of cyclic sulphites.

(*a*) Ethylene sulphite; (*b*) propylene sulphite; (*c*) 3-chloropropylene sulphite; (*d*) trimethylene sulphite; (*e*) 1 : 3-butylene sulphite; (*f*) sulphite A; (*g*) sulphite B; (*h*) cyclic sulphite from 5β-cholestane-3β : 5-diol.

1 : 2-Sulphites			1 : 3-Sulphites				
(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)	(*g*)	(*h*)
—	—	—	611w	620w	614w	611w	—
—	—	—	622m	635m	628m	623m	—
—	—	—	—	—	670w	666w	—
672s	675m	678m	675s	—	689m	674s	—
—	—	696m	708s	690m	—	700s	—
—	—	733m	—	724m	730s	—	—
744s	742m	—	749m	—	—	—	—
—	—	768m	—	—	—	—	—
—	—	—	—	822m	816w	818w	—
—	830m	—	—	—	826w	828m	—
—	—	843m	855s	846w	848s	838s	—
875w	—	—	—	—	—	870m	—
—	—	—	—	—	—	880w	—
—	—	888w	—	888s	—	886w	—
921s	—	—	904w	—	917w	927w	—
—	—	—	935s	934w	—	—	—
965m	969s	962s	—	952s	969s	—	—
—	—	—	—	974w	998m	986m	—
1011s	—	1026m	1019s	1017m	—	1008s	1001s
—	1061m	1050m	—	1061m	—	1078m	1048m
1090w	—	1078w	—	—	—	1087s	1097s
—	1105w	1106w	—	—	—	—	—
1128w	1141w	—	1141w	1133w	1122s	—	—
—	—	—	—	1153w	1153w	1152w	1159w
—	—	—	—	—	1160w	1184m	1177m
—	—	—	1190s	1195s	1188s	1189s	1192s
1214s	1215s	1213s	—	—	—	—	—
—	—	—	1234m	1230w	1239m	1230m	—
—	—	—	—	1250w	—	—	—
—	—	—	1277m	—	1274m	1288s	—
—	1308w	1298w	—	1315w	—	1303m	—
—	—	—	—	1333w	1330m	—	—
1362m	1385m	—	1367m	1387m	1388m	—	—
—	—	1428m	1428s	—	—	1448m	—
1472s	—	1454m	1467m	1467m	1467m	1467m	—

s = strong; m = medium; w = weak.

was cooled to −12°, and pyridine (1 ml.) and thionyl chloride (0·75 ml.) were added. The mixture was kept for 36 hr. at room temperature and then cooled to 0°, and ice, water, and ether were added. The ethereal solution was washed with water, dilute sodium hydrogen carbonate solution, and water again, dried (Na_2SO_4) and evaporated. The residue (135 mg.) was chromatographed on alumina (acid-washed, activity II; 4 g.). The bulk of the material was eluted

[8] Plattner, Segre, and Ernst, *Helv. Chim. Acta*, 1947, **30**, 1432.
[9] Plattner, Heusser, and Kulkarni, *ibid.*, 1948, **31**, 1885.

with light petroleum (b. p. 40—60°) containing 10% or 20% of benzene. After crystallisation from pentane, the *sulphite* formed small prisms, m. p. 160—162° (a polymorphic form, prisms, m. p. 135—137°, was sometimes obtained from pentane or from methanol) (Found: C, 72·0; H, 10·2; S, 6·5. $C_{27}H_{44}O_3S$ requires C, 72·0; H, 10·2; S, 7·1%); $[\alpha]_D$ +4·5° (*c* 1·4 in $CHCl_3$), $[M]_D$ +20°.

Other Cyclic Sulphites.—These were prepared by refluxing the appropriate diol with thionyl chloride. The products, which were washed with water, dried (K_2CO_3), and fractionated, had the following properties: ethylene sulphite,[1] b. p. 90°/42 mm., n_D^{25} 1·4448; propylene sulphite,[10] b. p. 92°/40 mm., n_D^{25} 1·4354; trimethylene sulphite,[2] b. p. 90—91°/38 mm., n_D^{25} 1·4498; cyclic sulphite[10] of (±)-butane-1 : 3-diol, b. p. 59°/10 mm., n_D^{25} 1·4437. We are indebted to Mr. D. J. Phillips for the preparation of the last compound.

Infrared Spectra.—These were recorded with a Hilger D209 spectrometer, used as a single-beam instrument. The liquids were placed between rock-salt or potassium bromide windows, depending on the region being scanned. The solids A and B were melted, then placed between the appropriate windows, and allowed to crystallise before their spectra were recorded. No washers were used, the films being of capillary thickness. The cyclic sulphite of 5β-cholestane-3β : 5-diol was examined only in the region 1000—1300 cm.$^{-1}$, as a crystalline film obtained by evaporation of a solution in carbon disulphide.

The spectral maxima are recorded in the Table. A number of bands, recorded in the region 3000 cm.$^{-1}$, result presumably from C–H vibrations and have not been included.

Discussion

That the compounds A and B are cyclic sulphites is proved by analysis, in conjunction with the facts that neither chlorine nor sulphur dioxide is readily displaced in acidic or neutral hydrolysis, whereas sulphite ion is rapidly and quantitatively liberated in alkaline solution at room temperature. The possibility of rearrangement during the reaction of the diol with thionyl chloride, giving 3-chloropropylene sulphite, is unlikely on *a priori* grounds, for one would not expect carbon–oxygen fission during the condensation. Rearrangement is made still more unlikely by the fact that the latter sulphite can be prepared independently and has properties different from those of A, B, or a mixture of A and B.

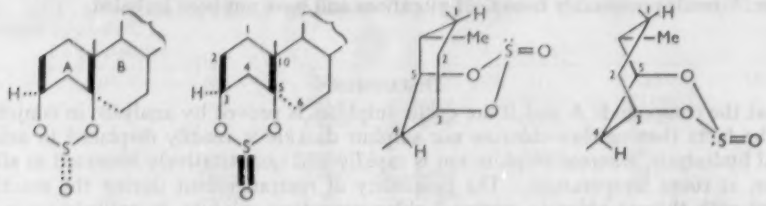
The infrared absorption spectra give conclusive evidence that A and B are indeed 1 : 3-sulphites. First, the 1 : 2-sulphites, including 3-chloropropylene sulphite, have no absorption bands in the region 600—640 cm.$^{-1}$. The simple 1 : 3-sulphites, however, including A and B, have a characteristic weak band at 610—620 cm.$^{-1}$, and another of medium intensity at 620—635 cm.$^{-1}$. These bands, which have similar contours, can, from their low frequencies, be attributed most plausibly to vibrations of the six-membered ring. Their absence in the more rigid 5-membered ring-structure is on this basis not surprising. Secondly, all the 1 : 2-sulphites, including 3-chloropropylene sulphite, have a strong absorption band at about 1214 cm.$^{-1}$, almost certainly to be attributed to the S=O stretching frequency, which customarily appears in this region.[11] The 1 : 3-sulphites, including the compounds A and B, also have a similar band, but it is consistently displaced by about 25 cm.$^{-1}$, to about 1190 cm.$^{-1}$.

From these facts, it is deduced that compounds A and B, prepared from 2-chloropropane-1 : 3-diol, are 1 : 3-sulphites, obtained without rearrangement. The conformational arrangement of the C–Cl bonds in these compounds can be assigned with a fair degree of certainty. For such bonds, it has been established that higher stretching frequencies are to be associated with equatorial than with axial substituents. This was first shown by Larnaudie,[12] who investigated a number of substituted *cyclo*hexanes, including the chloro-*cyclo*hexanes. Recent work by Barton, Page, and Shoppee,[13] to whom we are indebted for details made available to us before publication, has confirmed this generalisation by comparison of the spectra of a large number of isomeric pairs of halogeno-steroids. For the compounds investigated in this work, the strong absorption bands, at 730 cm.$^{-1}$ for A and at 700 cm.$^{-1}$ for B, can very reasonably be identified as C–Cl stretching frequencies,

[10] Myles and Pritchard, U.S.P. 2,465,915; *Chem. Abs.*, 1949, **43**, 4853.
[11] Vogel-Högler, *Acta Phys. Austriaca*, 1948, **1**, 328; Barnard, Fabian, and Koch, *J.*, 1949, 2442
[12] Larnaudie, *Compt. rend.*, 1952, **235**, 154; 1953, **236**, 909.
[13] Barton, Page, and Shoppee, *J.*, 1956, 331.

since, in the chloro*cyclo*hexanes, equatorial and axial C–Cl bonds have frequencies of absorption in these regions, and separated, in isomeric pairs, by about this amount.[12, 13] It seems very probable, therefore, that compound A has an equatorial C–Cl bond, and compound B has an axial C–Cl bond; and it seems likely that both of these compounds, in the crystalline state, exist substantially in one conformation.

All the simple 1 : 3-sulphites have absorption bands, which may reasonably be attributed to the S=O stretching frequency, at about 1190 cm.$^{-1}$. The cyclic sulphite prepared from 5β-cholestane-3β : 5-diol also has a strong absorption band at 1192 cm.$^{-1}$, almost identical with those observed in the spectra of the other 1 : 3-sulphites : it must have configuration (I) or (II), where the sulphite-containing ring is represented as in the plane of the paper : the S=O bond is *trans* in (I), and *cis* in (II), to the bridge formed by the remainder of the steroid A-ring. For each configuration, two conformations are possible, with the sulphite ring in the chair or boat form respectively. The two preferred conformations are (I; chair) and (II; boat), shown in perspective as (I*A*) and (II*A*) respectively, in each of which the S=O bond is equatorial. In the other two conformations, (I; boat) and (II; chair), the axial position of the S=O group would involve a prohibitively large

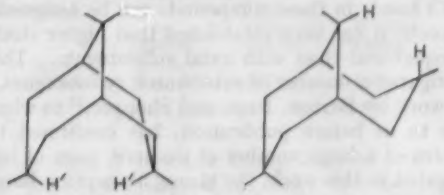


(I) (II) (I*A*) (II*A*)

repulsion between the oxygen atom and the 4β- or 1β-hydrogen atom respectively. Hence, whichever geometrical isomer (I or II) has been obtained, the S=O bond must be equatorial.*

It must now be considered whether the nearly identical position of the S=O absorption band in compounds A and B, and in the other 1 : 3-sulphites including the cyclic sulphite from 5β-cholestane-3β : 5-diol, can be taken as evidence that the conformational arrangement of the S=O linkage is the same in all these compounds. For substituted steroids, absorption-frequency differences of similar magnitude between axial and equatorial

* The possibility should be noted that in the *bicyclo*[3 : 3 : 1]nonane system (III) and its relevant hetero-analogues, of which the above cyclic sulphite is an example, one of the two rings may in general exist in a boat form (III*B*). For one of the major factors considered to contribute to the instability of boats in simple *cyclo*hexane derivatives is the repulsion between the two " flagpole " hydrogen atoms (written as H, H in formula III*B*), 1·83 Å apart.[14] In the two-chair conformation (III*A*), however, the distance between the two hydrogen atoms H′, H′ is only about 1·2 Å, and so (III*A*) is likely to be less stable than (III*B*), which may be the preferred conformation. Nitrogen-containing analogues of this steric type belonging to the sparteine series have recently been discussed.[15]



(III*A*) (III*B*)

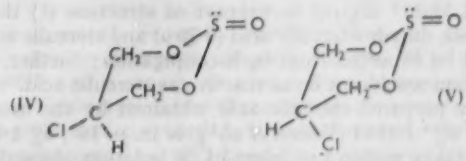
[14] Angyal and Mills, *Rev. Pure Appl. Chem.* (*Australia*), 1952, **2**, 185.
[15] Leonard, Thomas, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 1552; cf. Lewis and Shoppee, *J.*, 1956, 313.

substituents have been established for the chloro-, bromo-, iodo-, hydroxy-, methoxy-, acetoxy-, and deutero-substituents.[13, 16-18] A theoretical interpretation has been given [13, 16] for the direction of this difference, namely, that in the stretching vibration of an equatorial bond the motion of the ring-atom corresponds essentially with the stretching and compression of the six-membered ring, whereas, for an axial substituent, bending of the ring is involved. This would be expected to lead to a higher frequency for the stretching of the equatorial than of the axial bond, since the forces resisting ring-stretching and -compression are greater than those opposing ring-bending.

There seems to be no reason why the same principle should not apply to the S=O group, the infrared absorption characteristics of which are known to be markedly affected by change in the environment of the bond.[11] However, since as yet no definite evidence has been given concerning the absorption frequency to be associated with the stretching of axial S=O groups, the possibility exists that axial and equatorial S=O groups, in sulphites, should be assigned the same absorption frequency.

We prefer the alternative opinion, however, that all the 1 : 3-sulphites described in this paper have the S=O bond in the equatorial conformation. To assign the configurations of the isomeric 2-chlorotrimethylene sulphites on this basis, it has to be considered whether chair or boat conformations are most likely in these systems. In these sulphites, repulsions between " flagpole " hydrogen atoms are absent. On the other hand, both the C–Cl and the S=O group are strongly dipolar. Electrostatic interactions would, therefore, tend to keep these groups apart, and make boat forms unstable with respect to chair forms. Analogously, the chair predominates over the boat form in *cyclo*hexane-1 : 4-dione [19] by the ratio of approximately 9 : 1. We consider, therefore, that similar repulsions would make chair forms preferred to boat forms in the cyclic sulphites under consideration.

If the above assumptions are well founded, then the sulphite A, m. p. 42°, is the diequatorial *trans*-2-chlorotrimethylene sulphite (IV), and the isomer B, m. p. 62°, is *cis*-2-chlorotrimethylene sulphite (V) with the chlorine substituent axial and the S=O group equatorial. We propose this as a tentative assignment of the configurations of these compounds.



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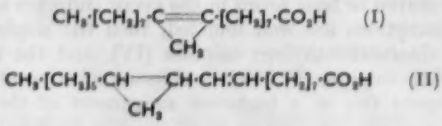
[16] Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571.
[17] Page, *J.*, 1955, 2017.
[18] Corey, Sneen, Danaher, Young, and Rutledge, *Chem. and Ind.*, 1954, 1294.
[19] Le Fèvre and Le Fèvre, *J.*, 1935, 1696.

356. *The Structure of Sterculic Acid.*

By P. K. Faure and J. C. Smith.

Infrared data support the conclusion that the sterculic acid molecule contains a *cyclo*propene ring,[1] which appears to be characterised by a strong absorption near 9·92 μ and a weak absorption near 5·35 μ. The infrared absorption band at 6·09 μ on which Verma, Nath, and Aggarwal base their formula for the acid is absent from freshly prepared specimens. The instability of the free acid appears to be due to the opening of this ring across the single bonds by interaction with the carboxyl group. Additional chemical evidence is presented for the production of 9 : 11-dioxononadecanoic acid on ozonolysis of sterculic acid. All the evidence is consistent with the structure ω-(2-*n*-octyl*cyclo*prop-1-enyl)octanoic acid for sterculic acid.

The structure of sterculic acid was suggested by Nunn[1] as ω-(2-*n*-octyl*cyclo*prop-1-enyl)octanoic acid (I). Infrared measurements were used to confirm the presence of a *cyclo*propane ring in dihydrosterculic acid, but the structure was deduced entirely from chemical evidence. Disregarding the latter, Verma, Nath, and Aggarwal[2] have considered structure (I) to lack supporting evidence in the fixing of the position of the double bond, which they have tried to do more exactly by means of the infrared spectrum of sterculic acid itself. They found bands at 9·96 μ and 6·09 μ, in the regions characteristic of *cyclo*propane derivatives and of C=C double bonds, respectively, and proposed the alternative structure (II), in which the three-membered ring and double bond form a " conjugated "



system. Dijkstra and Duin[3] argued in support of structure (I) that the difference in absorption noted between dihydrosterculic acid (9·79 μ) and sterculic acid (9·91 μ) is greater than that which would be expected from such conjugation; further, it is in the opposite direction. Such a system would not be as reactive as sterculic acid.

A sample of freshly prepared sterculic acid, obtained by the urea-complex method,[1] had m. p. 18·2—18·3°, $n_D^{24\cdot6}$ 1·4643 (Verma *et al.*[2] give m. p. 19°, n_D^{25} 1·4758). The infrared spectrum of this acid, taken within two hours of its isolation, showed a very strong band at 9·92 μ, but no band at 6·09 μ. When the acid was kept at 20—25° a band appeared at 6·07 μ; after 20 days this band was very distinct whereas the band in the 9·9 μ region had then almost completely disappeared. A specimen which had been kept for 32 days was a colourless viscous liquid, $n_D^{23\cdot6}$ 1·4801, equiv. 4780; its spectrum was identical with that of the sample kept for 20 days. The shift of wavelength from 9·92 μ to 9·80 μ found on conversion of sterculic acid into dihydrosterculic acid was accompanied by about 50% diminution in intensity. Both bands lie within the region 9·8—10·0 μ proposed by Derfer, Pickett, and Boord[4] as characteristic for *cyclo*propane groups, but Slabey,[5] from a study of 34 compounds containing this ring, found the maximum absorption at 9·79 ± 0·04 μ in all but the two cases of a monosubstituted ring, and generally at slightly lower wavelengths when two ring-hydrogens were replaced. The spectrum of dihydrosterculic acid was the same as that recorded by Hofmann *et al.*,[6] who showed conclusively that the band at 9·80 μ was due to the presence of the *cyclo*propane ring by comparison with the spectra of two synthetic long-chain acids containing such a ring.

Although the *cyclo*propane ring appears an improbable structure from the viewpoint

[1] Nunn, *J.*, 1952, 313.
[2] Verma, Nath, and Aggarwal, *Nature*, 1955, **175**, 84.
[3] Dijkstra and Duin, *ibid.*, 1955, **176**, 71.
[4] Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482.
[5] Slabey, *ibid.*, 1954, **76**, 3604.
[6] Hofmann, Jucker, Miller, Young, and Tausig, *ibid.*, p. 1799.

of bent bonds, Walsh [7] has predicted theoretically that such a structure is possible and stable. In this ring, because of its smallness, the two double-bonded carbon atoms are virtually linked by a third bond through the intermediate carbon atom, and one would expect from general considerations that the strain on the C=C link and its bonding force would be intermediate between those of the normal ethylenic and of the acetylenic linkages. Dunitz, Feldman, and Schomaker [8] have measured this interatomic distance in *cyclo*propene by an electron-diffraction method as $1{\cdot}28_6 \pm 0{\cdot}04$ Å, which lies between the normal bond lengths of 1·35 Å for C=C in ethylene and 1·20 Å for C≡C in acetylene.[9] It seems reasonable, therefore, to suppose that the stretching-vibration frequency of the C=C bond in a *cyclo*propene group will be intermediate between that of an ethylenic and of an acetylenic bond, and that the presence of such a ring will result in a band somewhere between 6·1 μ and 4·6 μ where these respective absorptions usually occur.[10, 11] The actual position of the *cyclo*propene vibration will, of course, depend to some extent on the nature of the substituent groups. Such a band was found in the spectrum of fresh sterculic acid at 5·35 μ, in a spectral region which is usually very empty. The band was quite distinct, though not very intense (about 7% absorption for an approximately 1·9% w/v solution in carbon disulphide in a 0·5 mm. cell). However, a strong band would not be expected here because of the symmetrical placing of the ring in the molecule.[12] This band cannot result from conjugation of a *cyclo*propane ring with a C=C double bond, since aliphatic conjugation usually shifts the absorption to slightly longer wavelengths and enhances the intensity.[13]

Although the *cyclo*propene group is a possible stable structure, it would be expected to be fairly reactive. That the rapid polymerisation of sterculic acid is associated with the presence of this ring and involves its destruction is readily seen from the infrared spectrum of the polymerised material, in which the band at 5·35 μ has completely disappeared and only a very weak absorption still remains near 9·9 μ. The carboxyl group also takes part in this reaction. This is borne out by the high equivalent weight of the polymerised material, and by the infrared spectrum, in which the very broad absorption between 3 and 4 μ, the broad, strong band at 10·7 μ, and the band at 7·78 μ, all of which are characteristic of fatty acid spectra and are associated with the presence of the carboxylic acid group,[14] have disappeared. From the spectrum it seems that an ester has been formed, for the C=C stretching absorption has shifted from 5·86 μ in the acid to 5·76 μ in the polymerised material, and a strong, new band has appeared at 8·58 μ. Both these bands, and the shift in C=O absorption, are characteristic of esters and lactones.[15] Nunn [1] has suggested that sterculic acid polymerises by reaction of the carboxyl group with the double bond, but the appearance of a double-bond absorption band at 6·07 μ in the spectrum of the polymerised material which is not present in the fresh sterculic acid spectrum, together with an increase in the methyl-group absorption [16] at 7·27 μ, indicates that the reaction occurs by splitting of the C–C linkages and opening of the ring. It seems most unlikely that the three-membered ring in the conjugated structure (II) would be opened by reaction with the carboxyl group at room temperature, when even fully conjugated acids such as octadeca-9 : 11-dienoic acid are fairly stable.

The key compound in Nunn's chemical evidence [1] for structure (I) was the dioxo-acid obtained by hydrogenation of the ozonide formed from sterculic acid, and deduced to be 9 : 11-dioxononadecanoic acid (III). This compound would not be produced on ozonolysis of structure (II). Its identification as (III) depended on its ultraviolet absorption spectrum,

[7] Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179.
[8] Dunitz, Feldman, and Schomaker, *J. Chem. Phys.*, 1952, **20**, 1708.
[9] Herzberg, "Infrared and Raman Spectra," van Nostrand Co. Inc., New York, 1945, pp. 398, 439.
[10] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, pp. 31, 49.
[11] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397; Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Substances," van Nostrand Co. Inc., New York, 1949.
[12] Ref. 10, p. 34.
[13] Ref. 10, p. 35.
[14] Sinclair, McKay, and Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 2570.
[15] Ref. 10, p. 153.
[16] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.

its reaction with ferric chloride, and on its oxidative degradation to the expected fragments. Additional chemical evidence of the correctness of this structure has now been obtained. The infrared spectrum of a new sample showed a very broad, strong band at 6·24 μ, which is characteristic of β-diketones in the enolised form.[16] The dioxo-acid and its ethyl ester gave an intense red colour with alcoholic ferric chloride, and the ester yielded a light-blue copper derivative, m. p. 90—92°, crystallising easily from methanol and very soluble in cold benzene. Alkaline hydrolysis of the dioxo-acid (III) should yield four products :

$$CH_3\cdot[CH_2]_7\cdot CO\cdot CH_2\cdot CO\cdot[CH_2]_7\cdot CO_2H \quad \text{(III)}$$

KOH ↓ KOH ↓

(IV) $CH_3\cdot[CH_2]_7\cdot CO\cdot CH_3$ $CH_3\cdot[CH_2]_7\cdot CO_2H$ (VI)

(V) $+ CO_2H\cdot[CH_2]_7\cdot CO_2H$ $+ CH_3\cdot CO\cdot[CH_2]_7\cdot CO_2H$ (VII)

Of these, methyl *n*-octyl ketone (IV), azelaic acid (V), and 9-oxodecanoic acid (VII) have now been isolated and identified.

All the spectral and chemical evidence which exists with regard to sterculic acid supports the originally proposed structure (I).

Experimental

M. p.s are corrected.

Isolation of Sterculic Acid.—*Sterculia foetida* seeds were obtained from the Forest Research Institute, Bogor, Indonesia. The pulverised kernels (*ca.* 58% of total seed) yielded a yellow oil (48%) when stirred with five portions of warm *iso*hexane (*ca.* 40°). The oil was saponified, and the acids liberated with concentrated hydrochloric acid were converted into their urea complexes, from which the sterculic acid was eventually isolated.[1] The acid, crystallised from acetone, had m. p. 18·2—18·3°, $n_D^{24\cdot6}$ 1·4643. It polymerised rapidly to a colourless, syrupy liquid : a sample left at room temperature (20—25°) for 32 days had $n_D^{23\cdot6}$ 1·4801, equiv., 4780.

Preparation of 9 : 11-*Dioxononadecanoic Acid.*—Sterculic acid was ozonised in cold ethyl acetate, the ozonide then hydrogenated in the presence of 30% palladised charcoal, and from this mixture 9 : 11-dioxononadecanoic acid (III) was isolated *via* the sodium salt.[1] The acid crystallised from hexane in plates, m. p. 59·6—59·9° (Found : C, 69·9; H, 10·5. Calc. for $C_{19}H_{34}O_4$: C, 69·9; H, 10·5%). Nunn[1] reported long needles, m. p. 57·5—58·3°. It gave an intense red colour with alcoholic ferric chloride.

Ethyl ester. In one preparation of the dioxo-acid the solution in ethyl acetate had to be left for 2 days, and it was decided to complete the esterification. Ethanol and a drop of concentrated sulphuric acid were added and the mixture left for 4 days. The resulting neutral product melted at 18° and gave an intense red colour with alcoholic ferric chloride. Reaction with copper acetate in methanol produced a grey-green precipitate which, crystallised from methanol (green solution), gave a light-blue solid, m. p. 90—92° (Found : Cu, 8·3. $C_{42}H_{74}O_8Cu$ requires Cu, 8·2%). This *copper derivative* was very soluble in cold benzene, but not soluble in chloroform, with which it appeared to react when warmed; hydrochloric acid regenerated the ester, m. p. 19°.

Alkaline Hydrolysis of 9 : 11-*Dioxononadecanoic Acid* (III).—The sodium salt (1·4 g.) was heated under reflux with potassium hydroxide (1·0 g.) in 50% ethanol (10 ml.); during 30 min. water (11 ml.) was added, and the mixture was left simmering overnight. The sweet-smelling layer, isolated by extraction with pentane, was an oil of m. p. 2° (0·21 g.). Rupe and Willi[17] gave 2·5° as the m. p. of methyl *n*-octyl ketone (IV). Our ketone (0·21 g.) was heated with *p*-nitrophenylhydrazine (0·165 g.) in ethyl alcohol (2 ml.) near the b. p., and 1 drop of acetic acid added. The orange precipitate, recrystallised from hexane–ethyl acetate, gave bright yellow crystals, m. p. 94·5—96° (Found : C, 66·5; H, 8·6. $C_{16}H_{26}O_2N_2$ requires C, 66·0; H, 8·6%). A specimen of methyl *n*-octyl ketone prepared according to Rupe and Willi's method,[17] melted at 2·3° and gave a p-*nitrophenylhydrazone*, m. p. 96—97·5°. A mixture of the two samples melted at 94·5—96·5°.

The alkaline solution (above) which had been extracted with pentane was acidified and the

[17] Rupe and Willi, *Helv. Chim. Acta*, 1932, **15**, 842.

liberated acids were extracted with ether; the ethereal extract was shaken for 17 hr. with a saturated solution of sodium hydrogen sulphite and set aside for 2 days. From the precipitated crystals of the bisulphite addition compound, a keto-acid (0·4 g.), m. p. 20°, was obtained. The semicarbazone behaved similarly to that of 9-oxodecanoic acid as described by Barger, Robinson, and Smith:[18] it first melted over a range 110—130° (from ethyl acetate) but, when heated to 80° for 4 hr. in a vacuum, it lost 13·8% of its weight and then melted at 120—130°. Barger, Robinson, and Smith[18] recorded m. p. 127° (Found: C, 54·2; H, 8·5; N, 17·3%; equiv., 245·4. Calc. for $C_{11}H_{21}O_3N_3$: C, 54·3; H, 8·7; N, 17·3%; equiv., 243·3).

The ethereal layer of the filtrate from the bisulphite addition compound was separated, washed with water, dried, and evaporated: a soft mass of crystals remained. After being washed with pentane and then with warm water, the residue was crystallised from hot water, yielding plates, m. p. 105—106° alone or when mixed with an authentic specimen of azelaic acid (Found: C, 57·6; H, 8·6%; equiv., 94·7. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%; equiv., 94·1).

Infrared Spectra.—These were recorded on a Perkin-Elmer Model 21 double-beam spectrophotometer with sodium chloride optics. The spectra of all the substances were taken in both carbon disulphide and tetrachloroethylene solutions (about 1·5—2% w/w in a 0·5 mm. cell) in order to cover the complete range from 2 to 15 μ.

We thank the Scientific and Research Department, ISCOR, Pretoria, for the use of their infrared spectrometer, and Dr. D. A. Sutton for helpful discussions. One of us (J. C. S.) is indebted to the Royal Society and the Nuffield Foundation for a Commonwealth Bursary which enabled him to take part in this investigation. This paper is published with the permission of the South African Council for Scientific and Industrial Research.

National Chemical Research Laboratory,
Pretoria, South Africa. [*Received, November 22nd,* 1955.]

[18] Barger, Robinson, and Smith, *J.*, 1937, 718.

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357. *The Atom Polarisation of Some Co-ordination Compounds of Metals.*

By (Mrs.) J. Macqueen and J. W. Smith.

The dielectric constants, specific volumes, and refractive indices of benzene or dioxan solutions of the aluminium and the ferric complex of acetylacetone, the beryllium and the ferric derivative of dibenzoylmethane, and of a number of *trans*-planar complexes of copper and nickel have been measured at 25°. The differences between P_2 and $[R_D]$ derived from these results are interpreted as atom polarisations arising principally from bending vibrations in which the chelate rings act as units. By making certain assumptions regarding the effective electric moments of the vibrating units, the apparent force constants of these vibrations have been calculated. The results are discussed in relation to the flexibility of the molecule, and arguments are given in favour of their interpretation as atom polarisation rather than as arising from the presence of permanent dipole moments in the molecules as a whole.

In 1932 it was observed [1] that the molecular polarisations (P) of basic beryllium acetate and the acetylacetone complex of beryllium in benzene or carbon tetrachloride solution exceed their molecular refractions ($[R]$) by about 30 c.c. As evidence had been obtained that some other compounds with highly dipolar bonds, such as co-ordinate linkages, had rather large atom polarisations ($_AP$), and since crystal-structure measurements indicated that the basic beryllium acetate molecule is symmetrical, it was suggested that the $P - [R]$ differences were due to high $_AP$ values, and not to the presence of permanent dipole moments in the molecules.

Although initially this interpretation was not generally accepted, confirmation of the

[1] Smith and Angus, *Proc. Roy. Soc.*, 1932, *A*, **137**, 372.

results was obtained when Finn, Hampson, and Sutton [2] obtained similar $P - [R]$ differences for acetylacetone complexes of beryllium and other metals in various solvents. Coop and Sutton [3] showed that these differences also exist in the vapour state, and, from exhaustive consideration of factors which might give rise to them, it was inferred that the original explanation was correct.

The Sellmeier dispersion equation, statistical arguments,[4] and simple geometrical treatment of the mechanics of the molecules [5] all indicate that ${}_AP$ can be expressed in terms of the force constants (k) associated with the various modes of vibration of the molecules and the effective charges (e_a) displaced during these vibrations by the relation:

$$ {}_AP = \sum_i (4\pi N e_{a_i}^2/9k_i) $$

Hence the largest contributions to ${}_AP$ come from the vibrations of low force constant, and, in the absence of low-frequency torsional vibrations, these will be bending vibrations. For a single such bending vibration the contribution to ${}_AP$ is $4\pi N e_{a_i}^2/9k_i = 4\pi N e_{a_i}^2 R_i^2/9R_i^2 k_i = 4\pi N \mu_i^2/9k_{bi}$, where R_i is the effective length of the vibrating system, k_{bi} is the force constant of the bending vibration in erg/radian^2, and μ_i is the electric moment of the vibrating unit. Hence, if the molecule has one type of bending vibration with a particularly low force constant, ${}_AP$ is given very closely by ${}_AP = 4\pi z N \mu_1^2/9k_b$ where z is the number of degenerate one-dimensional vibrational modes of this type associated with the molecule.

Coop and Sutton [3] pointed out that for the metal–acetylacetone complexes the vibrations likely to determine the value of ${}_AP$ are those associated with the vibration of the rings, as units, relative to the remainder of the molecule. In tetrahedral, octahedral, and cubic complexes, therefore, the chelate groups can be regarded as acting as **2**, **3**, and **4** one-dimensional vibrators, respectively. Hence, if the force constants k_b and electric moments μ_1 associated with the ring systems are of the same order of magnitude in each case, the ${}_AP$ values for these three groups of compounds would be expected to be approximately in the ratio **2 : 3 : 4**. The experimental results show this to be the case.

Since systematic studies of compounds of this type have been largely confined to the metal–acetylacetone complexes, polarisation measurements have now been made on solutions of other co-ordination compounds in which similar behaviour is to be expected. In the absence of the possibility of studying them in the vapour state, it would have been preferable to use only carbon tetrachloride or benzene as solvent for these compounds. Only a few of them, however, are sufficiently soluble in these solvents to permit their study with any reasonable degree of accuracy; but it has been found that for co-ordination compounds studied both in benzene and in dioxan only slightly higher P_2 and $P_2 - [R_D]$ values are obtained when the latter solvent is used. The range of compounds investigated has therefore been extended by using dioxan as solvent when the solubility in benzene was found to be too low for useful measurements to be made. The compounds now studied include the aluminium and the ferric complex with acetylacetone, the beryllium and the ferric derivative of dibenzoylmethane, and a number of planar complexes of copper and nickel.

The direct determination of the molecular refractions of some of these compounds proved difficult. In many cases the solutions were highly coloured, a factor which not only rendered the refractive index measurements difficult, but also threw doubt upon the value of the results owing to the incidence of anomalous dispersion. In such cases, therefore, the $[R_D]$ values have been calculated from the molecular refractions of the parent organic compounds, the contributions from the metal atoms and the bonds associated with them being taken as the mean values found for these contributions in compounds for which the measurements did not seem to be vitiated by anomalous dispersion: the allowance made was 12 c.c. for both copper and nickel.

The results are summarised in Table 1, where α, β, and γ are the limiting values of

[2] Finn, Hampson, and Sutton, *J.*, 1938, 1254.
[3] Coop and Sutton, *J.* 1938, 1269.
[4] Davidson and Sutton, *J.*, 1939, 347.
[5] Barriol and Regnier, *J. Chim. phys.*, 1952, **49**, 213.

$d\varepsilon/dw$, dv/dw, and dn^2/dw, respectively, at zero concentrations. $[R_D]$ values calculated as described above are shown in square brackets.

The measurements on aluminium and ferric complexes with acetylacetone confirm those of Finn, Hampson, and Sutton,[2] especially in showing that for the latter compound ${}_AP$ is rather greater than would be expected from the values for other compounds of the type

TABLE 1. *Summary of polarisation data.*

Compound	Solvent	$10^3\alpha$	$-10^3\beta$	$10^5\gamma$	$P_{2\infty}$ (c.c.)	R_D (c.c.)	$P_{2\infty} - R_D$ (c.c.)
Aluminium–acetylacetone	Benzene	861	310	140	133	88	45
	Dioxan	1121	121	317	139	88	51
Ferric–acetylacetone	Benzene	1056	373	281	151	99	52
	Dioxan	1337	190	448	158	99	59
Beryllium–dibenzoylmethane	Benzene	910	343	564	187	156	31
	Dioxan	1130	159	795	192	159	33
Ferric–dibenzoylmethane	Benzene	1130	386	525	318	238	80
	Dioxan	1440	187	745	336	242	94
Aluminium–diethyl malonate	Benzene	754	288	−50	200	120	80
trans-Copper–salicylaldehyde	Dioxan	2000	356	625	154	82 [86]	68
trans-Copper–salicylidenemethylamine	Dioxan	1562	273	534	153	91	62
trans-Copper–salicylidene-*p*-chloroaniline	Dioxan	1180	297	630	204	147 [151]	53
trans-Copper–salicylidene-*p*-bromoaniline	Dioxan	994	390	570	203	154 [157]	46
trans-Copper–salicylidene-*p*-iodoaniline	Dioxan	965	429	559	224	169 [169]	55
trans-Copper–3-hydroxy-1 : 3-diphenyltriazen	Dioxan	860	267	770	168	155 [155]	13
trans-Copper–salicylaldoxime	Dioxan	858	350	470	108	81 [86]	22
trans-Nickel–salicylaldoxime	Dioxan	1127	373	440	117	76 [86]	31
trans-Nickel–phenylazo-*p*-cresol	Benzene	879	418	—	175	[149]	26
trans-Nickel–2-phenylazopyrrole	Benzene	791	491	—	137	[116]	21

$M(acac)_3$. Coop and Sutton [3] attributed this to either a large effective moment of the vibrating unit or a small force constant, both of which effects would follow if the bonds to the central atom were unusually polar in character. It is of interest, therefore, that the $P_2 - [R_D]$ value for ferric complex of dibenzoylmethane is much greater even than that for the acetylacetone complex. That this is not due to a large additional moment within the ligand is shown by the fact that the ${}_AP$ value for the beryllium complex of dibenzoylmethane is almost the same as for that with acetylacetone. This result, therefore, seems to support Coop and Sutton's explanation, since the more highly polarisable dibenzoylmethane structure would tend to favour an increased polarity in the bonds to the central atom. It was impossible to follow this matter further, as the other metallic derivatives of dibenzoylmethane which were prepared were too sparingly soluble to permit their study.

For aluminium-diethyl malonate the difference between P_2 and $[R_D]$ is appreciably greater than for other complexes of aluminium, and hence it probably includes a contribution from orientation polarisation arising from rotation of the ethoxy-groups. The $P_2 - [R_D]$ differences for the planar complexes of copper and nickel are much smaller than would correspond with the orientation polarisation of the *cis*-compounds, and can therefore be interpreted as being the ${}_AP$ values for the *trans*-modifications, confirming the general conclusion that when only one form of a complex can be isolated this is usually the *trans*-modification.

In order to calculate the force constants for the vibration of the rings as units it is necessary to make some assumptions regarding the effective dipole moments of the vibrating groups. For this purpose the value (7·5 D) assumed by Coop and Sutton [3] in calculating the force constants for the acetylacetone complexes has been taken as a basis. By assuming the bonds to the central atom to be similar in each case, the modifications to this value introduced through the replacement of oxygen by nitrogen, and by the addition of polar substituents, have been assessed from the appropriate bond and group moments.

As was done by Coop and Sutton, the chelate groups in the tetrahedral and octahedral complexes have been regarded as acting as two and three one-dimensional vibrators, respectively. In the planar complexes, however, the vibrations of the two rings involve a

folding or twisting of the molecule as a whole, so they have been treated as single one-dimensional vibrators. As $k_b = 4\pi z N \mu_1^2 / 9_A P$, it follows, by insertion of the values of the universal constants, that $k_b = 0{\cdot}841 \times 10^{-12} \times z\mu_1^2/{}_A P$ erg/radian^2, where μ_1 is expressed in D and ${}_A P$ in c.c.

The values of μ_1 assumed for the various compounds and the apparent values of the vibrational force constants derived from them are shown in Table 2, which also includes a similar interpretation of previous measurements on analogous compounds. In computing the values of ${}_A P$ for the *trans*-forms of the nickel–glyoxime complexes, allowance has been made for the contributions to the molecular refraction of the nickel atom and of the bonds

TABLE 2. *Atom polarisations and bending force constants for co-ordination compounds.*

Compound	${}_A P$ (c.c.)	Ref.	μ_1 (D)	$10^{12} k_b$ (erg/radian^2)
Beryllium–acetylacetone	24	1	7·5	3·9
	27	2	7·5	3·5
Beryllium–dibenzoylmethane	31	*	7·5	3·1
Aluminium–acetylacetone	40	2	7·5	3·6
	45	*	7·5	3·2
Ferric–acetylacetone	57	2	7·5	2·5
	52	*	7·5	2·8
Ferric–dibenzoylmethane	80	*	7·5	1·8
Chromium–acetylacetone	40	2	7·5	3·6
Cobaltic–acetylacetone	30	2	7·5	4·5
trans-Copper–salicylaldehyde	68	*	7·5	0·7
trans-Copper–salicylidenemethylamine	54	7	7·2	0·8
	62	*	7·2	0·7
trans-Copper–salicylidene-*p*-chloroaniline	53	*	6·7	0·7
trans-Copper–salicylidene-*p*-bromoaniline	46	*	6·7	0·8
trans-Copper–salicylidene-*p*-iodoaniline	55	*	6·8	0·7
trans-Copper–3-hydroxy-1 : 3-diphenyltriazen	13	*	5·0	1·5
trans-Copper–salicylaldoxime	22	*	7·2	2·0
trans-Nickel–salicylaldoxime	31	*	7·2	1·4
trans-Nickel–phenylazo-*p*-cresol	26	*	5·3	0·9
trans-Nickel–2-phenylazopyrrole	21	*	6·6	1·8
trans-Nickel–methyl-*n*-propylglyoxime	28	6	7·8	1·7
trans-Nickel–methyl-*n*-butylglyoxime	24	6	7·8	2·0
trans-Nickel–benzylmethylglyoxime	23	6	7·8	2·1

* Present work.

associated with it. The figures used, therefore, are 12 c.c. less than the $P_{2\infty} - [R_D]$ values recorded by Cavell and Sugden.[6]

The results for the aluminium– and the ferric–acetylacetone compound are in fair agreement with previous data, whilst, in spite of the greater molecular weight of beryllium–dibenzoylmethane, its force constant falls in line with the values found for various acetylacetone complexes. This observation seems to confirm the essential validity of Coop and Sutton's suggestion that the major contributor to the atom polarisation is the vibration of the rings as relatively rigid units.

The planar compounds so far studied fall into two distinct classes, with force constants lying within the ranges 0·7—0·9 and 1·4—2·1 erg/radian^2, respectively. The latter group includes all the five-membered ring complexes studied, together with the salicylaldoxime derivatives of copper and nickel. Their ${}_A P$ values are commensurate with those of tetrahedral complexes. This circumstance, and the fact that although the rings are of very different types the force constants derived are all of the same order, appear to justify the assumption that the rings are essentially coplanar, the main contributions to ${}_A P$ arising from the vibrations of the rings as units. Unlike the acetylacetone and dibenzoylmethane derivatives, the rings in some of these compounds are not symmetrical, and so their moments will not act exactly along the bisector of the angle made by their bonds to the central atom. The method of treatment holds good, however, if k_b is interpreted as the force constant with respect to the distortion of the angle between the ring dipoles.

[6] Cavell and Sugden, *J.*, 1935, 621.
[7] Charles and Freiser, *J. Amer. Chem. Soc.*, 1951, **73**, 5223.

The six-membered ring systems, on the other hand, may not be strictly planar and hence vibrational modes other than the symmetrical vibrations of the two rings may be involved. Such increased flexibility of the system may account for the fact that the ${}_{A}P$ values for these compounds are generally much greater than for those containing five-membered rings. The salicylaldoxime complexes seem to be exceptional, but it is possible

TABLE 3. *Polarisation data.*

10^6w	$10^4\Delta\varepsilon$	$-10^5\Delta v$	$10^4\Delta n$
Aluminium–acetylacetone in benzene			
6028	52	188	3
13,448	115	423	6
19,036	165	584	9
27,889	237	861	13
34,396	293	1067	16
49,313	432	1522	23
Aluminium–acetylacetone in dioxan			
7470	80	97	8
15,269	158	180	17
21,998	242	278	24
28,771	313	350	32
34,787	392	425	39
56,832	631	698	64
5235	60	71	5
11,188	123	—	11
14,906	172	180	16
25,070	281	302	28
34,811	393	427	40
36,839	418	444	41
Aluminium–diethyl malonate in benzene			
8741	69	294	— 2
15,905	116	468	— 4
19,940	153	571	— 5
25,179	183	727	— 5
30,793	237	878	— 5
Copper–salicylaldehyde in dioxan			
1407	24	53	3
2027	40	76	5
3662	69	128	8
4559	93	164	10
5847	119	209	12
6643	132	236	15
Copper–3-hydroxy-1 : 3-diphenyltriazen in dioxan			
4551	39	101	13
9841	85	259	25
13,678	119	370	38
18,406	152	492	48
21,956	188	—	59
26,621	234	697	—
Nickel–salicylaldoxime in dioxan			
1856	21	—	3
3459	39	—	6
5057	58	187	8
6561	73	245	10

10^6w	$10^4\Delta\varepsilon$	$-10^5\Delta v$	$10^4\Delta n$
Ferric–acetylacetone in dioxan			
11,608	155	215	18
22,020	295	420	35
29,560	391	556	46
41,337	553	797	65
48,929	655	929	77
60,658	819	1152	96
Ferric–acetylacetone in benzene			
7485	80	266	7
16,940	177	636	16
32,196	339	1216	30
36,454	387	1369	34
42,257	447	1555	—
49,819	523	1860	—
Ferric–dibenzoylmethane in benzene			
2230	27	88	3
3750	39	144	5
5158	56	197	8
7420	85	295	13
8507	94	330	14
11,339	132	429	20
Copper–salicylidene-p-bromoaniline in dioxan			
2583	27	102	5
7334	75	288	14
9616	93	372	20
11,346	105	—	23
14,042	132	474	48
19,740	194	764	—
Copper–salicylidene-p-iodoaniline in dioxan			
2139	18	86	4
4966	39	204	10
6636	68	288	12
11,842	117	499	22
11,890	117	501	23
14,630	141	526	30
Copper–salicylaldoxime in dioxan			
3091	27	104	4
4879	44	176	6
7585	62	260	12
10,394	85	378	18
12,677	112	433	20
Nickel–2-phenylazopyrrole in benzene			
5914	47	285	—
9517	79	484	—
12,320	95	579	—
16,891	132	849	—

10^6w	$10^4\Delta\varepsilon$	$-10^5\Delta v$	$10^4\Delta n$
Beryllium–dibenzoylmethane in benzene			
4663	40	160	9
10,531	93	360	20
16,171	148	554	30
23,078	203	789	42
27,216	243	925	49
44,103	303	1520	89
Beryllium–dibenzoylmethane in dioxan			
3748	41	58	10
7977	92	127	22
9941	107	153	28
15,394	175	237	42
20,366	234	332	58
30,400	347	485	85
Ferric–dibenzoylmethane in dioxan			
1602	21	30	4
2680	40	50	7
4586	68	85	12
6242	87	118	16
7695	123	141	20
8731	226	165	23
Copper–salicylidene-p-chloroaniline in dioxan			
3603	42	101	7
7397	95	209	15
10,256	123	305	21
14,306	169	440	31
15,434	182	478	—
26,154	308	778	58
Copper–salicylidenemethylamine in dioxan			
3761	59	109	7
6601	—	177	12
9913	153	275	19
14,145	218	390	27
19,027	300	516	37
22,312	350	603	43
Nickel–phenylazo-p-cresol in benzene			
5086	46	221	—
10,128	85	423	—
14,821	128	619	—
20,250	178	859	—
22,213	198	909	—

that there may be hydrogen bonds bridging the oxygen atoms in the two rings, somewhat similar to those which occur in glyoxime complexes, which may "stiffen" the vibrating system by imposing a restriction upon the mode of vibration.

That the $P_2 - [R_D]$ differences for the other compounds containing six-membered rings may be due in part to a permanent dipole moment arising from a twisting of the rings out of the coplanar configuration cannot be entirely ruled out. If the whole were to be attributed to such a cause the resultant moments of the compounds studied would range from 1·0 to 1·8 D, whilst if the ${}_AP$ value is assumed to be about 30 c.c. in each case they would range from zero to 1·3 D. In view of the values assumed for the ring moments, the dipoles would need to be inclined at about 170° to lead to the results observed for most of the compounds. If each dipole were actually directed along the bisector of the angle between the linkages from the metal atom to the remainder of the molecule, however, a mere twisting of the molecule should not lead to a permanent moment. Although it is probable that the dipoles in these compounds are not directed along this axis, it is most unlikely that the permanent distortion of the molecule is sufficiently great to lead to this permanent moment.

The possibility of the molecule's undergoing a twisting vibration, however, is of some interest. If this is such that in each vibration it passes through the coplanar configuration, the $P_2 - [R_D]$ difference observed may validly be regarded as atom polarisation. On the other hand, if the coplanar configuration is a state of higher potential energy, so that the rings remain twisted in one sense for periods commensurate with the period of alternation of the field used in the measurements (10^{-6} sec.), the difference should be described as arising in part from a permanent dipole moment. The frequency (ν) of the vibrator is $\sqrt{(k_b/4\pi^2 m_r R^2)}$, where m_r is its effective reduced mass and R is its effective length. If these are expressed in atomic weight units and in Å, respectively, and k_b is expressed in units of 10^{-12} erg/radian^2, this becomes $\nu = 1{\cdot}23 \times 10^{13}\sqrt{(k_b/m_r R^2)}$. E, the energy hurdle which it can pass, on the average, 10^6 times per sec. is then given by $e^{-E/RT} = 10^6/\nu = 0{\cdot}8 \times 10^{-7}\sqrt{(m_r R^2/k_b)}$; E is 7·3 kcal. when $m_r R^2$ is about 3600 and k_b is unity, and wide variations in the values of these quantities do not alter this calculated value of E by more than $\pm 0{\cdot}5$ kcal.

It is very improbable that, in the compounds studied, the energy hurdle at the coplanar configuration is as high as this. The reactions leading to the formation of the compounds occur very readily, suggesting that, in the configuration of minimum energy, the potential energy arising from repulsion between the atoms of the two rings is not great. As this cannot be far displaced from the coplanar configuration it is unlikely, therefore, that the potential energy becomes very great in the latter state. In certain types of molecule, however, where larger groups have to come into close proximity in passing through the coplanar configuration, this might occur only about 10^6 times per sec. In cases of this type atom and orientation polarisation merge into one another.

Experimental

Materials.—Benzene was purified and dried as described previously.[8] Commercial "pure" dioxan was boiled with sodium until the metal remained bright, distilled, stored over sodium, and redistilled immediately before use.

Aluminium–acetylacetone, prepared by Young's method [9] and recrystallised from benzene and light petroleum (b. p. 80—100°), had m. p. 193°: Finn, Hampson, and Sutton [2] give m. p. 192—193°. The ferric complex of acetylacetone, prepared similarly and recrystallised from benzene, had m. p. 182°: Finn, Hampson, and Sutton give m. p. 181·3—182·3°. Beryllium–dibenzoylmethane, prepared by slow addition of aqueous beryllium sulphate to dibenzoylmethane in alcohol, and recrystallised from benzene and alcohol, had m. p. 214°: Booth and Pierce [10] give m. p. 214—215°. The *ferric complex* of dibenzoylmethane, prepared similarly

[8] Few and Smith, *J.*, 1949, 753.
[9] Young, *Inorg. Synth.*, 1946, **2**, 25.
[10] Booth and Pierce, *J. Phys. Chem.*, 1933, **37**, 59.

from ferric chloride, crystallised from benzene in dark red needles [Found: Fe, 7·65. $Fe(C_{15}H_{11}O_3)_3$ requires Fe, 7·70%]. Aluminium–diethyl malonate, prepared by Titschenko's method [11] and recrystallised from ether, formed white needles, m. p. 95°: Titschenko gives m. p. 94·5°.

trans-Copper- and nickel–salicylaldoxime were prepared by adding dilute aqueous-alcoholic salicylaldoxime to solutions of copper sulphate and nickel chloride, respectively, and were recrystallised from chloroform and dioxan. *trans*-Nickel–phenylazo-*p*-cresol, prepared by Elkins and Hunter's method [12] and repeatedly precipitated from chloroform solution by light petroleum (b. p. 80—100°), had m. p. 216°: Elkins and Hunter give m. p. 216°. *trans*-Nickel–2-phenylazopyrrole was prepared and purified by the method of Pfeiffer *et al.*[13] *trans*-Copper–salicylaldehyde was prepared by dropwise addition of alcoholic salicylaldoxime to a stirred solution of copper sulphate, and was recrystallised from dioxan. *trans*-Copper–salicylidenemethylimine, prepared by Pfeiffer and Glaser's method [14] and recrystallised from alcohol, had m. p. 158°: Pfeiffer and Glaser give m. p. 158°.

Copper–salicylideneaniline was prepared by adding excess of aqueous copper sulphate to the anil in alcohol, but after 5 recrystallisations from benzene and alcohol the dielectric constants and densities of its solutions in dioxan indicated that its molecular polarisation was 264 c.c. It was therefore the *cis*-modification or a mixture containing an appreciable proportion of that form. It formed deep brown star-shaped crystals [Found: Cu, 14·0. $Cu(C_{13}H_{10}ON)_2$ requires Cu, 13·9%]. The copper–salicylidene-*p*-halogenoanilines were prepared similarly. trans-*Copper–salicylidene*-p-*chloroaniline* formed copper-brown plates from benzene [Found: Cu, 12·0. $Cu(C_{13}H_9ONCl)_2$ requires Cu, 12·1%]. trans-*Copper–salicylidene*-p-*bromoaniline* formed golden-brown plates [Found: Cu, 10·2. $Cu(C_{13}H_9ONBr)_2$ requires Cu, 10·3%]. trans-*Copper–salicylidene*-p-*iodoaniline* formed lustrous coppery plates [Found: Cu, 9·0. $Cu(C_{13}H_9ONI)_2$ requires Cu, 9·0%]. Copper–3-hydroxy-1 : 3-diphenyltriazen, prepared by Elkins and Hunter's method,[15] had m. p. 191—192°: Elkins and Hunter give m. p. 190—192°.

Apparatus and Measurements.—The dielectric constants of the solutions relative to those of the solvents were determined with a heterodyne-beat apparatus.[16] Some of the refractive indices were determined with a Pulfrich refractometer and the remainder with a Hilger Abbé refractometer. Specific volumes were measured with a pyknometer. All measurements were made at 25·0°.

The results from which the parameters listed in Table 1 were derived are given in Table 3, where the symbols have their usual significance. For all these compounds ε, v, and n^2 were linear with w over the concentration range studied, and hence the slopes of the best straight lines through these values were taken as α, β, and ν, respectively. The values of $P_{2\infty}$ and $[R_D]$ deduced from these parameters were checked by comparison with the values of P_2 and $[R_D]$ calculated from the data for each concentration. There appeared to be no systematic variation of either P_2 or $[R_D]$ with concentration.

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Bedford College, Regent's Park, London, N.W.1. [*Received, November 24th, 1955.*]

[11] Titschenko, *J. Russ. Phys. Chem. Soc.*, 1899, **31**, 784.
[12] Elkins and Hunter, *J.*, 1935, 1598.
[13] Pfeiffer, Hesser, Pfitzner, Scholl, and Thielert, *J. prakt. Chem.*, 1937, **149**, 217.
[14] Pfeiffer and Glaser, *ibid.*, 1939, **153**, 265.
[15] Elkins and Hunter, *J.*, 1938, 1346.
[16] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.

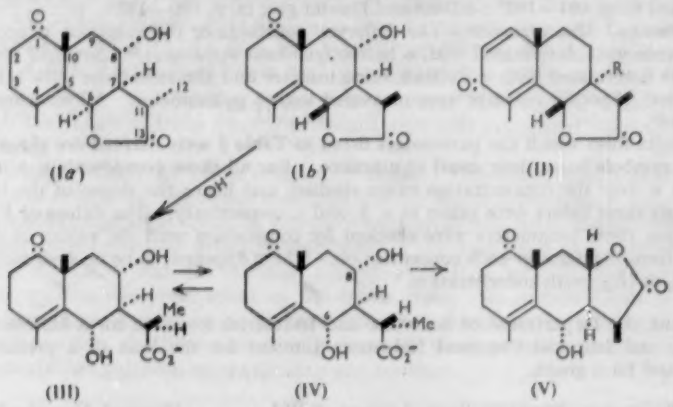
358. *The Chemistry of ψ-Santonin. Part X.**

By N. M. Chopra, Wesley Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart.

Revised structures are presented for ψ-santonic acid, (+)-β-desmotropo-ψ-santonin, and several related compounds. The stereochemistry of ψ-santonin and the reduction products of ψ-santonic acid are discussed.

(A) *Stereochemistry of ψ-Santonin.*—The structure of ψ-santonin has now been conclusively established [1,2] as (I), and recently we advanced the stereo-formula (I*a*) for it.[3] Independent evidence for the configurations shown in (I*a*) at $C_{(7)}$ and $C_{(8)}$ has been given by Dauben and Hance.[2] However, our evidence for the configuration at $C_{(8)}$ came from application of Klyne's rule [4] concerning the rotatory contribution of the potential hydroxyl group of the lactone ring and from the stability of the lactone in ψ-santonin. Klyne's rule, however, seems of doubtful validity when applied to lactones from allylic hydroxyl groups, as shown by its failure with santonin and 11β(H)-santonin.[5] Consequently, the *trans*-fused lactone of configuration (I*b*) becomes a possibility and evidence presented below shows that this structure explains the reactions of ψ-santonin better than (I*a*). Models of (I*b*) show that its stability should be at least equal to that of (I*a*).

ψ-Santonin is stable to potassium carbonate in boiling xylene, a reagent [6] which causes epimerisation of the 11-methyl group when in the unstable configuration. In the santonin (II; R = H) series the stable configurations have been shown by Cocker and McMurry [5]



(I*a*) (I*b*) (II)

(III) (IV) (V)

to be: (*a*) with a *cis*-fused butanolide, that in which the 11-methyl group is *cis* to the 7-hydrogen atom, and (*b*) with a *trans*-fused butanolide, that in which the 11-methyl group is *trans* to the 7-hydrogen atom. Corollaries to these rules are that: (*c*) when two *cis*-fused butanolides are possible, that in which the 11-methyl group is *cis* to the 7-hydrogen atom will be favoured; and (*d*) when two *trans*-fused butanolides are possible, that in which the 11-methyl group is *trans* to the 7-hydrogen atom will be favoured. Thus the rules (*a*) and (*b*) indicate that ψ-santonin has the configuration shown in (I*a*) or (I*b*) at $C_{(11)}$, according to whether it possesses a *cis*- or a *trans*-fused butanolide structure.

When ψ-santonin is heated with potassium hydroxide to 150—160° and subsequently

* Part IX, *J.*, 1955, 588.

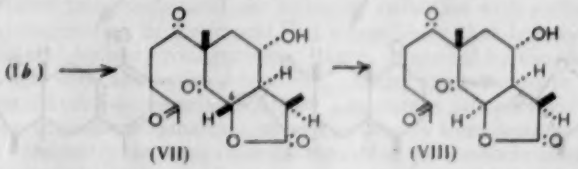
[1] Chopra, Cocker, Cross, Edward, Hayes, and Hutchinson, *J.*, 1955, 588.
[2] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[3] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1954, 1535.
[4] Klyne, *ibid.*, p. 1198.
[5] Cocker and McMurry, *J.*, 1955, 4430.
[6] Cocker, Cross, and Lipman, *J.*, 1949, 959.

acidified an isomeric, lævorotatory compound, *iso*-ψ-santonin is obtained. This is shown by its light-absorption characteristics to have the same functional groups as ψ-santonin. It shows a single maximum at 2890 Å (log ε 1·56) characteristic of an isolated keto-group, but its absorption at 2200 Å (log ε 3·4) is characteristic of a tetrasubstituted double bond. In the infrared spectrum, peaks shown by *iso*-ψ-santonin at 1758 (butanolide), 1700 (ketone), 1655 (C=C), and 3500 cm.$^{-1}$ (hydroxyl) are almost identical with those shown by ψ-santonin.[1] On the basis that ψ-santonin has the structure (I*b*), the procedure by which *iso*-ψ-santonin is made can be expected to lead *via* the ion (III) of the hydroxy-acid, to epimerisation at $C_{(11)}$ to form the ion (IV).[7] This altered configuration will, according to rule (*d*) above, cause lactonisation of (IV) to involve the hydroxyl at $C_{(8)}$ rather than that at $C_{(6)}$, so that *iso*-ψ-santonin will be the linear compound (V). This formulation is supported by the fact that *iso*-ψ-santonin is stable to potassium carbonate in boiling xylene; if in *iso*-ψ-santonin the original lactone ring of ψ-santonin were present the 11-methyl group would be in the unstable configuration. Further, the hydroxyl group of *iso*-ψ-santonin is much more resistant to oxidation by chromic acid than that of ψ-santonin,[2] as would be expected from its hindered position in (V). Its resistance to oxidation with manganese dioxide [8] in an inert solvent may probably be traced to the same cause.

A similar explanation for these changes is impossible on the basis of the formulation (I*a*) for ψ-santonin, since the 11-methyl group is already in the configuration of greater stability, regardless of whether lactonisation takes place at the 6- or the 8-hydroxyl group. Consequently the derived *iso*-ψ-santonin would have the 11-methyl group in the unstable configuration.

A consequence of the formulation of ψ-santonin as (I*b*) is that the configurations at $C_{(6)}$, $C_{(7)}$, and $C_{(11)}$ become identical with those of santonin (II; R = H) and artemisin (II; R = OH).[9] This would be expected on biogenetic grounds. For the same reason the β-configuration of the angular 10-methyl group would be expected :[3] this configuration has been found in many sesquiterpenes of the eudesmane type,[10] and is supported by rotational evidence given below.

The stereo-formula (I*b*) leads to the formula (VII) for the primary product (A) of ozonisation.[1] The change of this product (A) into the isomer (B) under very mild alkaline treatment [1] is probably the result of epimerisation at $C_{(6)}$ to give the more stable *cis*-fused

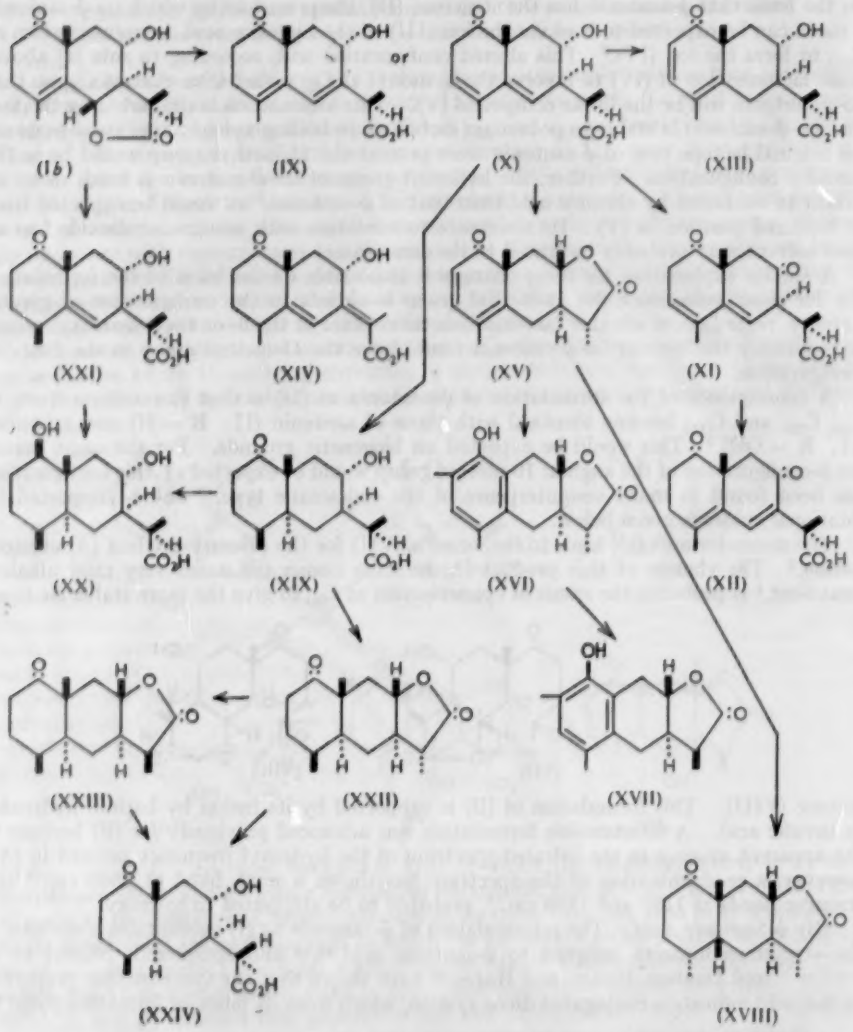


lactone (VIII). This formulation of (B) is supported by its fission by barium hydroxide to lævulic acid. A dibutanolide formulation was advanced previously for (B) because of the apparent absence in the infrared spectrum of the hydroxyl frequency present in (A); however, a re-examination of the spectrum has shown a weak band at 3540 cm.$^{-1}$ and stronger bands at 1152 and 1360 cm.$^{-1}$, probably to be attributed to hydroxyl.

(B) *ψ-Santonic Acid.*—The reformulation of ψ-santonin as (I) necessitates a revision of the structures hitherto assigned to ψ-santonic acid [11,12] and compounds related to it. Cocker [13] and Dauben, Hance, and Hayes [14] have shown that the spectroscopic properties of this acid indicate a conjugated diene system, which from its mode of formation could be

[7] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1955, 41.
[8] Ball, Goodwin, and Morton, *Biochem. J.*, 1948, **42**, 516; Sondheimer, Amendolla, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5930, 5932, with references therein to earlier work.
[9] Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044.
[10] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313; Barton and Tarlton, *J.*, 1954, 3492; Ayer and Taylor, *ibid.*, p. 3027; Howe and McQuillin, *J.*, 1955, 2423.
[11] Clemo and Cocker, *J.*, 1946, 39.
[12] Cocker and Lipman, *J.*, 1949, 1170.
[13] Cocker, *Chem. and Ind.*, 1955, 1484.
[14] Dauben, Hance, and Hayes, *J. Amer. Chem. Soc.*, 1955, **77**, 4609.

(IX) or (X). Dauben and his co-workers chose the latter structure, partly because they did not succeed in oxidising ψ-santonic acid with manganese dioxide. However, one of us has carried out this reaction. The product is undoubtedly the conjugated dienone (XII), having maximal absorption in ethanol at 3100 Å (log ε 3·77) in good agreement with the calculated value [15] (3140 Å). The functional groups are also indicated by infrared bands



(potassium bromide disc) at 1756 cm.$^{-1}$ (ketone) and at 1663, 1643, and 1616 cm.$^{-1}$ (conjugated dienone). Dauben and Hance [2] obtained an impure specimen of the methyl ester ($\varepsilon_{max.}$ 3070 Å in EtOH) of this acid (XII) by a different route. An impure disemicarbazone of (XII) showed maximal absorption at 2176 (log ε 4·21) and 3250 Å (log ε 3·70), characteristic of the semicarbazone of isolated ketone and of conjugated dienone systems respectively.

[15] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.

While this reaction has been considered as evidence for the allyl alcohol [8,13] structure (IX) of ψ-santonic acid, it is not conclusive because βγ-unsaturated alcohols are sometimes oxidised by manganese dioxide.[16] The primary oxidation product of the alcohol (X) would be the unconjugated dienone (XI), which could rearrange to (XII) during working up of the very slightly acidic reaction mixture. We now therefore consider that on balance the evidence favours formulation (X) rather than (IX) for ψ-santonic acid. In particular it explains [14] the slow base-catalysed isomerisation of ψ-santonic acid.[13] Unfortunately, the product is obtained pure only in very low yield, so that detailed examination of it has not been possible. However, its absorption ($\lambda_{max.}$ 3325 Å; log ε 3·56, in EtOH; infrared bands at 1653, 1627, and 1567 cm.$^{-1}$) is characteristic of a homoannular dienone system,[14] and suggests the structure (XIII), rather than its isomer, the unsaturated acid (XIV). Compound (XIII) would be formed by the base-catalysed isomerisation of (X) but not of (IX). Accordingly ψ-santonic acid (X) is 8α-hydroxy-1-oxoeudesma-3 : 5-dien-13-oic acid.[5]

If formula (X) is accepted, it becomes possible to deduce the stereochemistry of the various compounds derived from ψ-santonic acid.[13] Anhydro-ψ-santonic acid (XV) [13,14] must have a *trans*-fused lactone ring. Since this compound is converted into (+)-β-desmotropo-ψ-santonin [6] under conditions unlikely to cause any rearrangement,[17] it follows that the structure and stereochemistry of the latter is represented by (XVI). Its epimerisation to (+)-α-desmotropo-ψ-santonin [6] (XVII) would then be expected from rule (*b*) above. The stability of the *trans*-fused lactone of (+)-β-desmotropo-ψ-santonin is surprising; however, Corey and Sneem's [18] calculations seem to indicate that at this position a *trans*- is less strained than a *cis*-fused lactone.

The hydrogenation of anhydro-ψ-santonic acid (XV), like that of cholesta-2 : 4-diene,[19] would be expected to take place from the more accessible top side of the molecule, so that the tetrahydro-compound (XVIII) would have a *cis*-A/B ring fusion. On the other hand, the hydrogenation of ψ-santonic acid to tetrahydro-ψ-santonic acid (XIX) would be expected [20] to result in a *trans*-A/B ring fusion. Some support for the *trans*-configuration is given by negative shift in molecular rotation ($\Delta[M]_D$ −97°) in going from tetra- to hexahydro-ψ-santonic acid (XX); a similar shift is found in going from cholestan-1-one to cholestan-1α-ol ($\Delta[M]_D$ −304°) or -1β-ol ($\Delta[M]_D$ −356°).[21] Since the 1β(equatorial)-hydroxy-compound is produced from cholestan-1-one either by reduction with sodium in propanol or by catalytic hydrogenation in acetic acid,[21] it seems likely that hexahydro-ψ-santonic acid (XX) has also a 1β-hydroxy-configuration; this is supported by the identity of hexahydro-ψ-santonic acid with hexahydro-ψ-santonin. Under the latter name the compound was prepared from dihydro-ψ-santonin (XXI) by a two-stage process involving reduction of the ketone group with sodium amalgam, as well as directly from ψ-santonin by catalytic hydrogenation.[11] Evidently the usual rules distinguishing the stereochemistry of reduction by sodium and by catalytic hydrogen do not apply at the highly hindered 1-position.

The catalytic reduction of dihydro- (XXI) to hexahydro-ψ-santonin (XX) can be considered, from analogy with the hydrogenation of Δ^5-steroids, to be further evidence for the *trans*-A/B fusion in (XX).

Tetrahydro-ψ-santonic acid (XIX) is dehydrated by acetic anhydride to the lactone, α-anhydrotetrahydro-ψ-santonic acid, now formulated as (XXII). This accounts for the easy isomerisation to β-anhydrotetrahydro-ψ-santonic acid (XXIII) [rule (*b*)], and the

[6] The prefixes α- and β- were previously [6] used to denote compounds of lower and higher melting point respectively. They have no stereochemical significance. It is now proposed [5] to name the parent skeleton of the desmotropo-compounds simply desmotropo-ψ-santonin. (+)-β-Desmotropo-ψ-santonin (XVI) is thus 7α(H) : 8β(H) : 11β(H)-desmotropo-ψ-santonin; (+)α-desmotropo-ψ-santonin (XVII) differs from this only in configuration at $C_{(11)}$.

[16] Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62.
[17] Barton, *J. Org. Chem.*, 1950, **15**, 466.
[18] Corey and Sneem, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.
[19] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 252.
[20] Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567.
[21] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.

alkaline hydrolysis of both the α- and the β-compounds to a third, isomeric tetrahydro-ψ-santonic acid (XXIV), epimerisation of (XXII) at $C_{(11)}$ evidently taking place before hydrolysis.

The rotations of several compounds reported previously have been redetermined, and the values of the molecular rotations are shown below. In all cases lactonisation involving the 8-hydroxyl group leads to a negative shift in molecular rotation, in agreement with

	Lactone	Hydroxy-acid	$\Delta[M_D]$
iso-ψ-Santonin (V)	−308°	+24°*	−332°
Tetrahydroanhydro-ψ-santonic acid (XVIII)	+50	+313 *	−263
(+)-β-Desmotropo-ψ-santonin (XVI)	−132	+261	−393
α-Anhydrotetrahydro-ψ-santonic acid (XXII)	−332	+238	−570
β-Anhydrotetrahydro-ψ-santonic acid (XXIII)	−94	+295	−389
Anhydrohexahydro-ψ-santonic acid [lactone of (XX)]	−133 (acetate)	+162	(−295)

* K salt in dilute EtOH.

Klyne's rule.[4] The molecular rotation of the acetate of anhydrohexahydro-ψ-santonic acid is known, but not that of the parent 1-hydroxy-compound, which probably differs by about −50°, so that the $\Delta[M]_D$ of −295° is probably too small.

Investigation of the carbonyl stretching frequencies of the *trans*-fused lactones mentioned above shows that they vary from 1754 to 1777 cm.$^{-1}$.

Further work in the chemistry of ψ-santonin is halted because of the inaccessibility of this compound.

Experimental

ψ-Santonic Acid.—Concentrated hydrochloric acid (6 c.c.) was added with stirring to finely powdered ψ-santonin (2 g.), and more hydrochloric acid (up to 2 c.c.) was added to give a clear solution. When stirring was continued for a few minutes the required acid began to separate. It was collected (1·5 g.; m. p. 168—170°) and crystallised from alcohol as needles, m. p. 176°.[11] The acid before crystallisation is sufficiently pure for most purposes.

Oxidation of ψ-Santonic Acid.—*1 : 8-Dioxoeudesma-4 : 6-dien-13-oic acid* (XII). ψ-Santonic acid (0·7 g.), in chloroform (200 c.c.), was shaken for 3 days with manganese dioxide [6] (2 g.) at room temperature. After filtration and removal of solvent in a vacuum at 40—50° an oil was obtained, which solidified (0·5 g.; m. p. 150—155°) when rubbed with light petroleum. Crystallisation from ethyl acetate–light petroleum gave the *diketo-acid* as pale yellow needles, m. p. 171—172° (depressed to 150° with ψ-santonic acid), $[\alpha]_D^{26}$ +305° (*c*, 0·608 in $CHCl_3$), $\lambda_{max.}$ 3100 (infl. 3600) Å [log ε 3·75 (2·76) in EtOH] (Found : C, 68·7, 68·5; H, 7·1, 7·0. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). It gives a crude semicarbazone, m. p. *ca.* 220°. Its *tetrahydro*-compound, prepared by reduction in ethyl acetate over palladised charcoal, crystallised from ethyl acetate as colourless rhombs, m. p. 181°, $\lambda_{max.}$ 2910 Å (ε 41·8 in EtOH) (Found : C, 67·7; H, 8·6. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%).

The hydrate of tetrahydro-ψ-santonic acid,[12] m. p. 191—192°, had $[\alpha]_D^{25}$ +83·5° (in $CHCl_3$), $\lambda_{max.}$ 2920 Å (ε 54 in EtOH). It showed bands at 1709 (C=O and CO_2H) and 3618 cm.$^{-1}$ (hydroxyl).

Hexahydro-ψ-santonic acid (hexahydro-ψ-santonin),[11,13] m. p. 188—189°, had $[\alpha]_D^{19\cdot5}$ +56·1° (in $CHCl_3$). Its acetate (lactone), m. p. 126—126·5°, had $[\alpha]_D^{20}$ −45·2°. It showed bands at 1721 (acetate) and 1776 cm.$^{-1}$ (butanolide) in $CHCl_3$.

Isomerisation of ψ-Santonin.—A mixture of ψ-santonin (3 g.), potassium hydroxide (6 g.), and water (6 c.c.) was heated at 165—170° for 4 hr. The dark brown mixture was dissolved in water (50 c.c.) and extracted continuously for 48 hr. with benzene. The extract was decolorised with charcoal and concentrated, giving a solid (2 g.; m. p. 150—160°). Repeated crystallisation from benzene gave *iso-ψ-santonin* (0·2 g.) as needles, m. p. 205°, $[\alpha]_D^{16}$ −116·5° (*c* 0·25 in 1 : 1 water–ethanol) (Found : C, 68·2; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). Its solubility in water is greater than that of ψ-santonin.

Conversion of Anhydro-ψ-santonic Acid into (+)-β-Desmotropo-ψ-santonin.—The anhydro-compound (0·5 g.) was warmed at 48—55° for 4 hr. with a solution of concentrated sulphuric acid (2·5 c.c.) in water (3·7 c.c.). The product (0·5 g.; m. p. 145—150°) was collected. One crystallisation from dilute alcohol gave (+)-β-desmotropo-ψ-santonin (0·3 g.), m. p. 186° undepressed on admixture with an authentic specimen.[6]

Isolation of an Unidentified Degradation Product of ψ-Santonin.—Hydrolysis of the ozonisation product (A) (7·5 g.) with barium hydroxide as previously described [1] and distillation of the barium-free solution gave lævulic acid and a syrup which on long storage deposited colourless plates (0·1 g.), m. p. 199—202°. Crystallisation from water gave a *substance* (D), m. p. 209° (Found: C, 67·5; H, 6·4. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%).

The authors are grateful to Messrs. T. & H. Smith, Ltd., for supplies of ψ-santonin and other materials, and the Medical Research Council of Ireland for financial assistance.

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359. 1 : 2-3 : 4-8 : 9-10 : 11-*Tetrabenzopentacene*.

By E. CLAR, W. KELLY, and W. G. NIVEN.

Tetrabenzopentacene (III) has been synthesised from (*a*) 1:2:3:4:5:6:7:8-octahydrophenanthrene and (*b*) phenanthrene and pyromellitic anhydride. The mono- and the di-quinone of the hydrocarbon and its addition product with maleic anhydride have been prepared.

PYROMELLITIC ANHYDRIDE has been condensed twice with 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydrophenanthrene in the presence of aluminium chloride. The product, which is a mixture of (I) and the corresponding *iso*phthalic acid, was cyclised in a melt of sodium chloride and zinc chloride [cf. the cyclisation of *o*-(octahydro-9-phenanthroyl)benzoic acid [1]]. The product was not tetrahydrotetrabenzopentacene, as expected, but 6 : 13-dihydrotetrabenzopentacene (II), probably owing to oxidation by air during the reaction. A small quantity of the tetrabenzopentacene (III) which was also formed was removed during recrystallisation by the addition of some maleic anhydride.

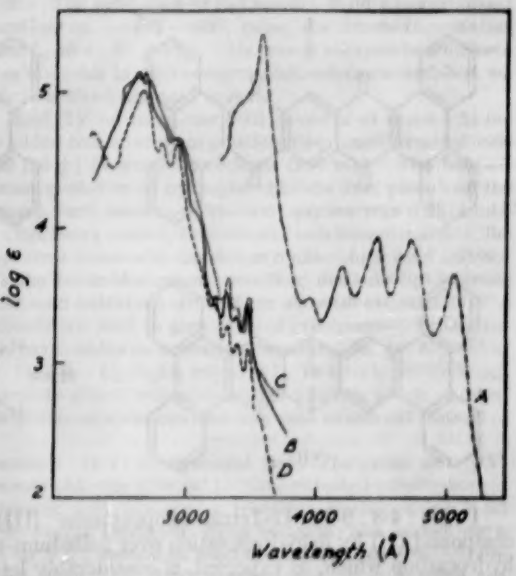
Absorption spectra of:

(*A*) 1 : 2-3 : 4-8 : 9-10 : 11-*Tetrabenzopentacene* (III) *in* 1-*methylnaphthalene*. *Max.* (Å; log ε *in parentheses*): 5050 (3·67), 4720 (3·93), 4470 (3·95), 4200 (3·73), 3950 (3·49), 3570 (5·41).

(*B*) 6 : 13-*Dihydro*-1 : 2-3 : 4-8 : 9-10 : 11-*tetrabenzopentacene* (II) *in dioxan*. *Max.*: 3470 (3·43), 3380 (3·34), 3310 (3·51), 2910 (4·66), 2680 (5·14), 2620 (5·12).

(*C*) *Dipotassium salt from the maleic anhydride adduct* (VII) *in alcohol*. *Max.*: 3480 (3·48), 3390 (3·40), 3330 (3·63), 2930 (4·66), 2700 (5·09), 2620 (5·15).

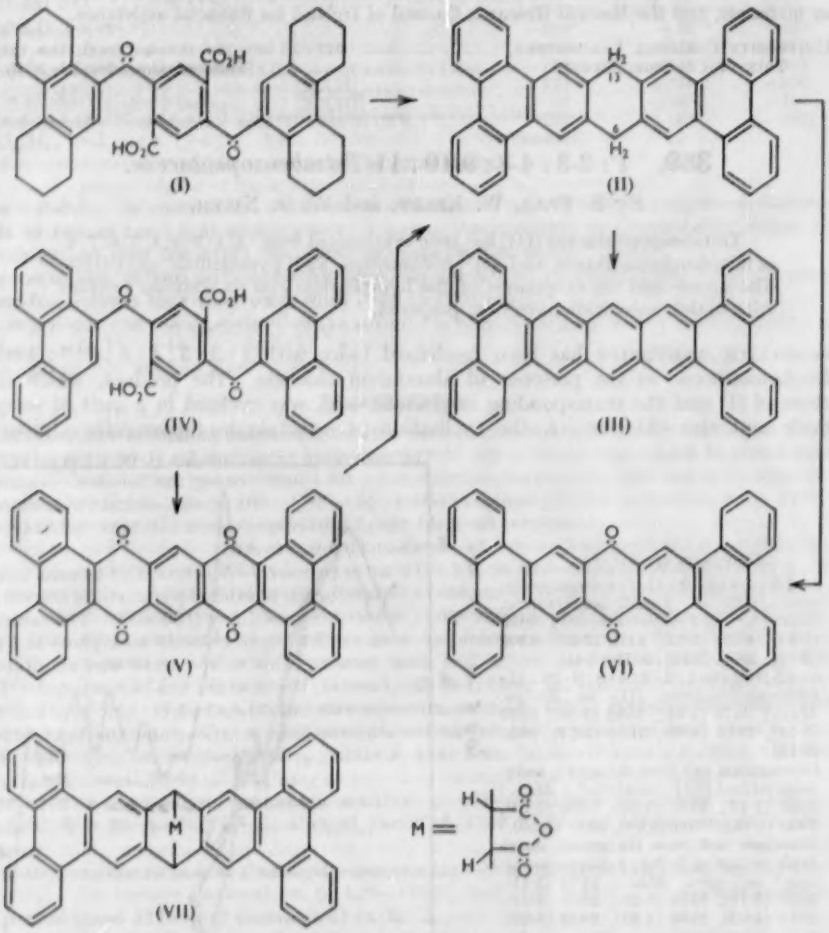
(*D*) *Disodium salt from the maleic anhydride adduct of* 1 : 2-3 : 4-*dibenzopentacene* [2] *in water*. *Max.*: 3470 (3·11), 3380 (3·16), 3310 (3·28), 3205 (3·51), 2915 (4·62), 2800 (4·63), 2650 (5·02).



[1] Clar, *J.*, 1949, 2168.

yield numerous isomers, only one dicarboxylic acid was obtained, being either the terephthalic acid (IV) or the isomeric isophthalic acid.

Ring closure with benzoyl chloride and sulphuric acid gave the diquinone (V) which was reduced by pyridine, zinc dust, and acetic acid to 6 : 13-dihydrotetrabenzopentacene (II). This was identical with the hydrocarbon obtained as above.



1 : 2-3 : 4-8 : 9-10 : 11-Tetrabenzopentacene (III) was obtained from the dihydro-compound (II) by dehydrogenation over palladium–charcoal at 370°. It is an orange-red hydrocarbon which, as expected, is considerably less reactive than pentacene, but it still reacted very quickly with maleic anhydride to form the colourless adduct (VII). The adduct and the dihydro-compound (II) contain the aromatic complexes of two triphenylene molecules, as shown by the close similarity (see Figure) between the absorption spectra of (II) and (VII), and that of the maleic anhydride adduct of 1 : 2-3 : 4-dibenzopentacene.[2]

The dihydro-compound (II) was oxidised by selenium dioxide in boiling nitrobenzene to the monoquinone (VI).

[2] Clar and Frommel, *Ber.*, 1948, **81**, 163.

Experimental

M. p.s were taken in evacuated capillaries. Microanalyses are by Mr. J. M. L. Cameron and Miss M. W. Christie.

Di-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-9-*phenanthroyl*)*benzenedicarboxylic Acids* (I and an isomer).—A mixture of the octahydrophenanthrene (21 g.), pyromellitic anhydride (11 g.), and powdered aluminium chloride (27 g.) was heated in tetrachloroethane (120 ml.). The reaction became vigorous at 60° and was continued until evolution of hydrogen chloride ceased, the final temperature being 80—85°. After the mixture had been cooled and decomposed, the tetrachloroethane solution was washed with dilute hydrochloric acid, then extracted several times with dilute aqueous ammonia, and the combined extracts were acidified with hydrochloric acid. The light fawn mixture of isomers (10 g.) crystallised with difficulty from nitrobenzene or acetic acid as a non-uniform powder of unsharp m. p. (Found : C, 78·2; H, 5·7. Calc. for $C_{36}H_{36}O_6$: C, 77·3; H, 6·5%). This product, in concentrated sulphuric acid, gave a brownish-yellow solution, which, on being heated, changed through brownish-orange to a light brown.

6 : 13-*Dihydro*-1 : 2-3 : 4-8 : 9-10 : 11-*tetrabenzopentacene* (II).—A mixture of powdered acid (I) (6 g.), sodium chloride (1·2 g.), and finely divided zinc chloride (6 g.) was heated to 330° during 10—15 min. The cooled solid melt was powdered and extracted with boiling dilute hydrochloric acid and then with hot dilute ammonia solution. The residue was dried and sublimed *in vacuo*. The orange sublimate crystallised from xylene as orange needles. When a small quantity of maleic anhydride was added during crystallisation, colourless needles, m. p. 426—428°, of the *dihydro-compound* (II) were obtained (Found : C, 94·8; H, 5·0. $C_{36}H_{24}$ requires C, 95·0; H, 5·0%). Before melting, the colourless crystals became pale orange and they melted to give a reddish-orange melt.

1 : 2-3 : 4-8 : 9-10 : 11-*Tetrabenzopentacene* (III).—The dihydro-compound (II) (0·1 g.) was sublimed *in vacuo* through an electrically heated tube of granulated palladium–charcoal (20%) in a slow stream of carbon dioxide at 370°. The sublimate of red needles (0·06 g.) crystallised from 1 : 2 : 4-trichlorobenzene in red needles, m. p. 498—499°, being the *tetrabenzopentacene* (Found : C, 95·4; H, 4·5. $C_{36}H_{22}$ requires C, 95·4; H, 4·6%). Its orange solution in trichlorobenzene had a green fluorescence. It was insoluble in cold concentrated sulphuric acid but, on being heated, dissolved to give a green solution which changed to red.

Di-9-*phenanthroylbenzenedicarboxylic Acid* (IV or an isomer).—A solution of phenanthrene (40 g.) in tetrachloroethane (150 ml.) was added to a mixture of powdered pyromellitic anhydride (22 g.) and powdered aluminium chloride (60 g.) in tetrachloroethane (150 ml.). The temperature was raised to 75°, at which a vigorous evolution of hydrogen chloride took place and the initial orange colour of the mixture became dark brown. This temperature was maintained for 30 min. with frequent shaking, and, after being cooled, the mixture was decomposed. The organic layer was separated and washed several times with hot dilute hydrochloric acid and hot water. Xylene (400 ml.) was added to the tetrachloroethane solution, and the light brown precipitate was washed with xylene, dried, and extracted with dilute aqueous ammonia. The ammonia solution was acidified with hydrochloric acid to give 34 g. of precipitate. Crystallisation from nitrobenzene several times gave uniform colourless needles, m. p. 377—378° (decomp.), of an *acid* (Found : C, 79·1; H, 3·9. $C_{36}H_{22}O_6$ requires C, 79·4; H, 3·9%) which dissolved in hot concentrated sulphuric acid to give a brownish-orange solution which changed to brownish-yellow. Similar results were obtained when benzene was used as solvent instead of tetrachloroethane.

1 : 2-3 : 4-8 : 9-10 : 11-*Tetrabenzopentacene*-5 : 14-7 : 12-*diquinone* (V).—The crude acid (IV) (10 g.) was heated under reflux with benzoyl chloride (200 ml.). Concentrated sulphuric acid was added dropwise. Each drop of sulphuric acid produced a transient green colour. Acid was added until the green colour was no longer produced. The solution was boiled for a further 10 min. Fine brownish-red needles (6 g.) separated from the boiling solution. These were sublimed *in vacuo* and recrystallised from 1 : 2 : 4-trichlorobenzene, to give small red needles, m. p. 486—487°, of the *diquinone* (V) (Found : C, 84·5; H, 3·2. $C_{36}H_{16}O_4$ requires C, 84·75; H, 3·4%). It gave a green colour in hot concentrated sulphuric acid; in alkaline sodium dithionite solution it gave a violet vat from which the diquinone could be recovered by shaking with air.

6 : 13-*Dihydro*-1 : 2-3 : 4-8 : 9-10 : 11-*tetrabenzopentacene* (II).—The diquinone (0·7 g.), zinc dust (10 g.), and pyridine (150 ml.) were heated under reflux and acetic acid (80%, 25 ml.) was added during 5 hr. The dark red solution quickly changed to a transiently violet one and then slowly from reddish-orange to pale yellow. Orange-yellow plates crystallised during the

reaction. After being filtered off, the crystals were separated from the zinc dust by treatment with hydrochloric acid. Sublimation of the residue *in vacuo* gave pale yellow crystals (0·15 g.). Crystallisation from xylene containing small amounts of maleic anhydride gave colourless needles of the hydrocarbon (II), m. p. 425—427° (Found: C, 94·9; H, 4·8%). There was no depression of the m. p. when this compound was mixed with the dihydro-compound obtained as above. The ultraviolet spectra of the two compounds were identical. Dilution of the pyridine mother-liquor, with water, from the above filtration yielded a further 0·3 g. of the dihydro-compound.

1 : 2-3 : 4-8 : 9-10 : 11-*Tetrabenzopentacene*-6 : 13-*quinone* (VI).—A solution of the dihydro-compound (II) (0·2 g.) in nitrobenzene (15 ml.) was heated under reflux with selenium dioxide (0·18 g.) for 30 min. The reddish-brown needles which crystallised during the reaction were filtered from the hot solution and sublimed *in vacuo*. The small quantity of selenium, mixed with the needles, sublimed at a much lower temperature and was easily separated from them. The sublimate crystallised from nitrobenzene in orange feathery needles, m. p. >550°, of the *quinone* (Found: C, 90·0; H, 4·0. $C_{38}H_{20}O_2$ requires C, 89·7; H, 4·0%). It gave a red solution in hot concentrated sulphuric acid. As with other pentacene quinones, it did not form a vat with alkaline sodium dithionite.

Maleic Anhydride Adduct (VII).—A suspension of the powdered hydrocarbon (III) (30 mg.) in xylene (20 ml.) was heated under reflux with excess of maleic anhydride until the hydrocarbon had dissolved and the solution had become a faint yellow colour. The *adduct* crystallised as colourless prisms which decomposed without melting above 310° to give the red hydrocarbon (Found: C, 87·0; H, 4·5. $C_{42}H_{24}O_3$ requires C, 87·5; H, 4·2%). It dissolved in warm concentrated sulphuric acid to give a blue solution which changed to purple.

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UNIVERSITY OF GLASGOW. [*Received, December 7th, 1955.*]

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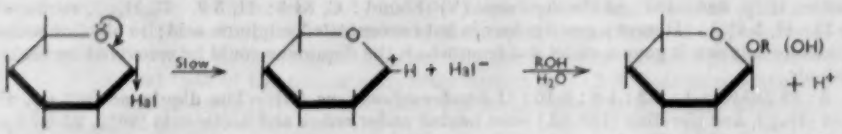
360. *The Reactivity of the O-Acylglycosyl Halides. Part IV.* The Solvolytic Reactions of O-Acetyl-α-D-glycosyl 1-Halides in the Presence of Electrophilic Catalysts.*

By G. L. MATTOK and G. O. PHILLIPS.

The rate of solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-halides in water–acetone and methanol–acetone in the presence of mercuric salts as catalyst, is proportional to the first power of both sugar halide and mercuric salt concentration. The mechanism postulated for the reaction involves the rate-determining formation of a carbonium-ion intermediate. In addition other features of this reaction such as salt effect, stereochemical form of the reaction, and solvent effects are similar to the uncatalysed S_N1 solvolysis of these compounds.

Hydrogen bromide can function as an electrophilic catalyst in a similar way to the mercuric salts, and this is discussed in relation to the autocatalysis by liberated hydrogen bromide which is a characteristic of non-catalysed solvolysis.

IN earlier papers of this Series, the mechanism of solvolysis of the *O*-acetylglycosyl 1-halides in polar solvents was described. The reactions are of type S_N1 with the rate-determining ionisation facilitated by an electron-release mechanism operating from the lactol-ring oxygen atom:



* Part III, *J.*, 1953, 2896.

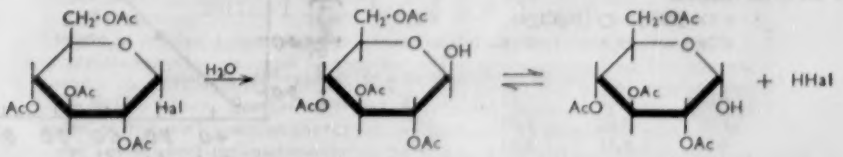
This view was opposed to that of Frush and Isbell,[1] who regarded the reactions as of the type S_N2. Lemieux and Huber,[2] however, support our results. They studied the solvolysis of 3 : 4 : 6-tri-*O*-acetyl-α- and -β-D-glucopyranosyl chloride in acetic acid, where the rate and stereochemical form of the reaction are unaffected by the addition of potassium acetate. Hassel and Ottar [3] examined the ring conformations necessary for the S_N2 mechanism in these compounds, and on this basis consider a bimolecular mechanism (S_N2) unlikely. In polar solvents, therefore, the S_N1 mechanism operating for the solvolytic reactions of tetra-*O*-acetyl-α-D-glucosyl 1-halides is the more probable. However, for certain reactions of these compounds where conditions are less favourable to the S_N1 mechanism, *e.g.*, low nucleophilic character of the reagent, low ionising power of the solvent, Chapman and Laird [4] report the incursion of bimolecular character, leading to an intermediate mechanism in some instances.

Considerable practical interest centres on the solvolytic reactions of *O*-acetylglycosyl 1-halides in polar media in the presence of electrophilic catalysts, and it was by this method that Koenigs and Knorr [5] first prepared glucosides. Under these conditions the reaction rates are considerably enhanced and the tendency for deacetylation of the molecule by the liberated halogen acid is decreased. In the present work mercuric salts were used as catalyst; here the medium is homogeneous throughout the reaction, thus eliminating the complications which arise when a precipitate is formed, *e.g.*, when silver salts are used as catalysts.

We have studied the mechanism of the catalysed solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-halides and compared this reaction with the uncatalysed unimolecular solvolysis of these compounds. The results suggest a close relation and enable also the autocatalysis by liberated hydrogen halides, characteristic of non-catalysed solvolyses, to be explained.

Results

Catalysed Reactions.—During the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-halides, inversion of configuration occurs, so formation of product can be followed polarimetrically. In aqueous solution, however, the over-all change of rotation is the result of two consecutive reactions. The initial solvolysis of the halide is followed by a slower mutarotation of the product,



which is most marked during the later stages of the reaction and in highly polar solvents. Fig. 1 shows the change in rotation with time for the hydrolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in acetone–water in the presence of mercuric bromide. The initial slope represents the formation of the β-tetra-*O*-acetylglucose. As the concentration of this compound builds up, the amount of mutarotation increases, and in the later stages this reaction predominates as shown by the final increase in rotation. Evaluation of the rate constant of the initial reaction by analysis of the curve is difficult because both reactions are catalysed by the liberated halogen acid. We have avoided these complications by extrapolating to zero time and calculating reaction rates from the initial slopes: this proved reliable and reproducible.

Order of the reaction. Measurement of the initial rates in acetone–water at 100°, in which the concentration of only one reactant was varied, showed the rate to be proportional to the first power of both halide and mercuric salt and independent of the concentration of water.

The results for tetra-*O*-acetyl-α-D-glucosyl 1-chloride are shown in Fig. 2 which gives the

[1] Frush and Isbell, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 161.
[2] Lemieux and Huber, *Canad. J. Chem.*, 1955, **33**, 128.
[3] Hassel and Ottar, *Acta Chem. Scand.*, 1941, **1**, 929.
[4] Chapman and Laird, *Chem. and Ind.*, 1954, 20.
[5] Koenigs and Knorr, *Ber.*, 1901, **34**, 95.

plots of log $(d\alpha/dt)_{t=0}$ against log $[HgCl_2]_{t=0}$ and log $[RCl]_{t=0}$. From the slope of the lines obtained it is seen that the rate is actually proportional to $[RCl]^{1\cdot01}$ and $[HgCl_2]^{1\cdot01}$. The rate was unaffected by the amount of water, in the range 1—4%, in aqueous acetone. We therefore calculated second-order rate constants by using the expression $(d\alpha/dt)_{t=0} = k_2[RCl][HgCl_2]$ and they are shown in Table 1.

For tetra-*O*-acetyl-α-D-glucosyl 1-bromide the results are similar (see Table 2).

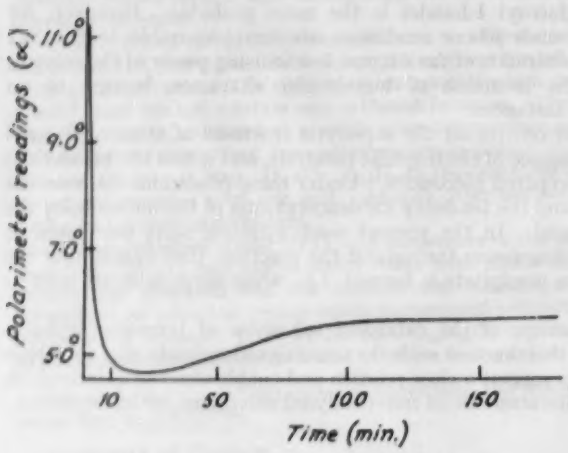


FIG. 1. *Hydrolysis of tetra-O-acetyl-α-glucosyl 1-bromide in 98% acetone–water, catalysed by mercuric bromide.*

$[RBr] = 0{\cdot}074$M.
$[HgBr_2] = 0{\cdot}052$M.

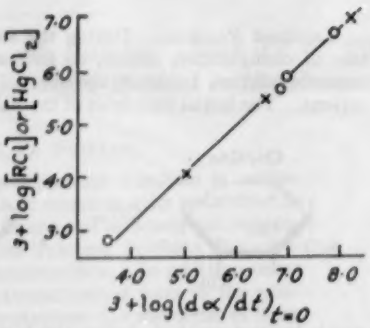


FIG. 2. *Solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in 98% acetone–water, catalysed by mercuric chloride. Order of the reaction.*

× [RCl]. ○ $[HgCl_2]$.

Effect of temperature and large variations of solvent. Although in the range 1—4% water in acetone, the rate is independent of the amount of water, larger proportions do affect the rate. Table 3 shows this for tetra-*O*-acetyl-α-D-glucosyl 1-chloride, and also the effect of temperature.

From the activation energies obtained we have calculated the thermodynamic constants of the reactions at the individual solvent concentrations (see Table 4).

Effect of addition of lithium chloride. Lithium chloride was added in the methanolysis of tetra-*O*-acetyl-α-D-glucosyl 1-chloride in acetone–methanol. The results are in Table 5.

Uncatalysed Solvolysis.—In the absence of mercuric chloride the solvolytic reactions of

TABLE 1. *Second-order rate constants for the solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in acetone–water catalysed by mercuric chloride, at* 100°.

$[RCl]$ $(10^3$M)	$[HgCl_2]$ $(10^3$M)	H_2O (%)	10^3k_2 (l. mole^{-1} sec.$^{-1}$)	$[RCl]$ $(10^3$M)	$[HgCl_2]$ $(10^3$M)	H_2O (%)	10^3k_2 (l. mole^{-1} sec.$^{-1}$)
5·005	3·875	2	3·70	4·985	1·915	2	3·31
5·00	3·695	2	3·79	4·97	6·40	1	3·75
5·00	4·72	2	3·71	5·10	4·57	4	3·85
3·57	4·965	2	3·73				

TABLE 2. *Second-order rate constants for the solvolysis of tetra-O-acetyl-α-D-glucosyl 1-bromide in 98% acetone–water catalysed by mercuric bromide at 25·2°.*

[RBr] (10^3M)	5·045	7·415	4·98
[$HgBr_2$] (10^3M)	3·54	5·19	7·414
10^4k_2 (l. mole^{-1} sec.$^{-1}$)	1·24	1·27	1·20

TABLE 3. *Solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in mixed solvents catalysed by mercuric salts.*

Acetone–water mixtures.

Water (%)	Temp.	k_2 (l. mole^{-1} sec.$^{-1}$)	E (kcal. mole^{-1})
2	100°	$3·70 \times 10^{-3}$	17·5
	74·5	$7·44 \times 10^{-4}$	
	61·3	$2·24 \times 10^{-4}$	
10	100	$9·35 \times 10^{-3}$	13·5
	76·4	$2·74 \times 10^{-3}$	
	69·1	$1·70 \times 10^{-3}$	
	59·2	$9·15 \times 10^{-4}$	
20	100	$1·11 \times 10^{-2}$	10·4
	74·5	$3·76 \times 10^{-3}$	
	66·0	$2·84 \times 10^{-3}$	
	61·3	$2·19 \times 10^{-3}$	
30	100	$2·50 \times 10^{-2}$	10·6
	76·4	$9·19 \times 10^{-3}$	
	69·1	$6·93 \times 10^{-3}$	
40	100	$3·43 \times 10^{-2}$	9·8
	69·6	$1·05 \times 10^{-2}$	
	62·9	$7·71 \times 10^{-3}$	
	58·5	$6·54 \times 10^{-3}$	

Acetone–methanol mixtures.

MeOH (%)	Temp.	k_2 (l. mole^{-1} sec.$^{-1}$)	E (kcal. mole^{-1})
10	133°	$1·13 \times 10^{-2}$	13·2
	100	$2·87 \times 10^{-3}$	
	77·7	$8·44 \times 10^{-4}$	
	67·4	$4·28 \times 10^{-4}$	
25	133	$1·87 \times 10^{-2}$	13·3
	100	$5·10 \times 10^{-3}$	
	77·3	$1·71 \times 10^{-3}$	
	67·4	$8·38 \times 10^{-4}$	
50	100	$5·83 \times 10^{-3}$	12·9
	77·8	$2·21 \times 10^{-3}$	
	67·4	$1·20 \times 10^{-3}$	
100	35·0	$2·60 \times 10^{-4}$	13·8
	31·5	$1·91 \times 10^{-4}$	
	26·8	$1·35 \times 10^{-4}$	
	25·2	$1·14 \times 10^{-4}$	

TABLE 4. *Free energies, entropies, and heats of activation for the solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in the presence of* 0·05M-$HgCl_2$, *at* 100°.

Catalysed hydrolysis (in acetone–water mixtures).

H_2O (%)	2	10	20	30	40
$\Delta G^{\ddagger}$ (kcal.)	26·3	25·6	25·6	24·9	24·7
$\Delta H^{\ddagger}$ (kcal.)	16·8	12·8	9·7	9·9	9·9
$\Delta S^{\ddagger}$ (e.u.)	−25·7	−34·6	−42·6	−40·3	−41·8

Catalysed methanolysis (in acetone–methanol mixtures).

% MeOH	10	25	50	100 *
$\Delta G^{\ddagger}$ (kcal.)	26·5	26·1	25·9	25·4
$\Delta H^{\ddagger}$ (kcal.)	12·5	12·6	12·2	13·0
$\Delta S^{\ddagger}$ (e.u.)	−37·7	−36·3	−36·9	−49·5

* Value obtained by extrapolation to 100°.

TABLE 5. *Effect of addition of lithium chloride: solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in 25% methanol–acetone in presence of* 0·05M-$HgCl_2$ *at* 100°.

[LiCl] (10^3M)	0	2·16	2·53	4·95
10^4k_2 (l. mole^{-1} sec.$^{-1}$)	5·10	4·60	3·94	1·79

TABLE 6. *Effect of variation of temperature and solvent on the solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in acetone–water.*

Temp.	10^4k_1 (sec.$^{-1}$)	E (kcal. mole^{-1})	Temp.	10^4k_1 (sec.$^{-1}$)	E (kcal. mole^{-1})	Temp.	10^4k_1 (sec.$^{-1}$)	E (kcal. mole^{-1})
	Water : 20%			Water : 30%			Water : 40%	
100°	59·7	20·0	100°	214·0	19·6	66·0	61·0	20·2
62·5	3·04		66·3	16·5		60·0	30·4	
55·2	1·50		55·2	5·72		50·1	13·1	
			50·1	4·64				

TABLE 7. *Free energies, entropies, and heats of activation for the solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride at 100° in acetone–water.*

Water (%)	20	30	40
$\Delta G^{\ddagger}$ (kcal.)	29·4	28·5	27·4
$\Delta H^{\ddagger}$ (kcal.)	19·3	18·9	19·5
$\Delta S^{\ddagger}$ (e.u.)	−27·2	−25·7	−21·4

TABLE 8. *Correlation of rates of solvolysis (extrapolated to 25°) of tetra-O-acetyl-α-D-glucosyl 1-chloride in acetone–water with Y values.*

Water (%)	20	30	40
Y value	−0·673	0·130	0·796
log k_1	−7·155	−6·635	−6·050

TABLE 9.

[HBr] (10^3M)	0	5·0	10·0	15·0	25·0
10^3k_1 (sec.$^{-1}$)	3·67	4·10	4·54	5·05	5·95

tetra-*O*-acetyl-α-D-glucosyl 1-chloride are of S_N1 type; for example, the reaction rate is unaffected by the addition of hydroxyl ions.[6]

We have extended previous studies on the uncatalysed solvolysis of this compound by measuring solvolysis rates in acetone–water at several temperatures. These and the activation energies are shown in Table 6. Winstein and Grunwald [7] correlated solvolysis rates with solvent properties by assigning to the solvent a characteristic constant (*Y* value). The authors are grateful to Professor Winstein for making available to them the *Y* values of acetone–water mixtures at 25°. On extrapolation of the results for tetra-*O*-acetyl-α-D-glucosyl 1-chloride to give the rates at 25°, the rate (k) can be correlated with the ionising power of the solvent. The plot of log k against *Y* is linear, which, represented by the relation $\log k = mY + \log k_0$, gives the characteristic constants $m = 0{\cdot}70$, $k_0 = -6{\cdot}69$ (Table 8).

The free energies, entropies, and heats of activation for the reaction were calculated and are shown in Table 7.

Autocatalysis by liberated hydrogen halides: addition of hydrogen bromide. Addition of anhydrous hydrogen bromide in the methanolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide (at 25°) increases the initial rate of reaction. The first-order solvolytic constants increase linearly with the concentration of added hydrogen bromide within the range 0—$2{\cdot}5 \times 10^{-3}$M (Table 9).

DISCUSSION

The solvolysis of alkyl halides in aqueous solvents, or alcohols, catalysed by metal salts has been extensively studied.[8,9,10] When silver salts are the catalysts in such reactions, the mechanism shows features similar to those of an S_N1 reaction; for example, Hughes and Ingold and their co-workers and others [9-12] have shown that the effect of constitutional changes, stereochemical form of the reaction, and nature of the products are closely related in the two instances. These results indicate that the reaction catalysed by silver salts and the S_N1 solvolysis proceed by way of the same intermediate carbonium ion; silver ions are the main catalytic agent, but there is also a rather indefinite contribution by the surface of the precipitated silver halides. As noted on p. 1837, this complication is avoided without altering the general course of the reaction, by use of mercuric salts as catalysts. Benfey,[13] and Hammett and Roberts,[14] found that, for the solvolysis of several organic

[6] Newth and Phillips, *J.*, 1953, 2896.
[7] Winstein and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 846.
[8] Senter, *J.*, 1910, **97**, 346; 1911, **99**, 95; Baker, *J.*, 1934, 987; Kappanna, *Proc. Indian Acad. Sci.*, 1935, **2**, 512.
[9] Hughes, Ingold, and Masterman, *J.*, 1937, 1236.
[10] Cowdrey, Hughes, and Ingold, *J.*, 1937, 1243.
[11] Whitmore, Whittle, and Popkin, *J. Amer. Chem. Soc.*, 1939, **61**, 1586.
[12] Dostrovsky and Hughes, *J.*, 1946, 169.
[13] Benfey, *J. Amer. Chem. Soc.*, 1948, **70**, 2165.
[14] Roberts and Hammett, *ibid.*, 1937, **59**, 1063.

bromides catalysed by mercuric nitrate, the rate is determined by formation of a carbonium-ion intermediate, the catalytic agent being mercuric ions : $Hg^{2+} + RX \longrightarrow HgX^+ + R^+$. Ingold [15] made a brief reference to unpublished work by Bunter, Hughes, and Ingold on the mercuric chloride-catalysed hydrolysis of 1-phenylethyl chloride; similarities to the S_N1 reaction are again evident, but catalysis here is by un-ionised mercuric salt. Our results on the kinetics of solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-halides catalysed by mercuric salts show that the rate-determining stage is dependent on the first power of the concentration of the halide and of the mercuric salt. The rate is independent of the reagent provided it is present only in low concentration and does not appreciably affect the dielectric properties of the medium. In the solvents used, acetone and alcohol, it is unlikely that the mercuric halides are dissociated, and catalysis will therefore be by the un-ionised salt. The mechanism may therefore be represented :

$$RX + HgX_2 \xrightarrow{\text{Slow}} R^+ + HgX_3^-$$

$$\underset{(HOH)}{R^+ + R'OH} \xrightarrow{\text{Fast}} \underset{(ROH)}{ROR'} + H^+$$

The catalyst facilitates the removal of the halide ion, and the rate of the catalysed reaction is considerably faster than that of the uncatalysed ionisation. The existence of the complex ion HgX_3^- is well established. Bayles, Bentley, A. G. Evans, and Jones [16] recently showed that when triphenylmethyl chloride and mercuric chloride are mixed in nitromethane the following equilibria are set up :

$$Ph_3C\text{-}Cl + HgCl_2 \rightleftharpoons PhC_3^+ HgCl_3^-$$

$$Ph_3C^+ HgCl_3^- \rightleftharpoons Ph_3C^+ + HgCl_3^-$$

The concentrations of these ions were also measured.

Lindberg [17] also found that the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in the presence of mercuric bromide was of the second order. This evidence is based on the analysis of the complete hydrolysis curve (Fig. 1), by allowing for the accompanying mutarotation. At best, this procedure can only be very approximate, especially when no allowance was made for catalysis of the main reaction by the liberated halogen acid. The method we have described is not dependent on Lindberg's assumptions regarding the mutarotation, and our rate constants are not in exact agreement with his; nevertheless, we are in accord with his general conclusion that the rate-determining step is the removal of the halogen to form the carbonium ion.

When lithium chloride is added in the catalysed solvolysis of tetra-*O*-α-D-glucosyl 1-chloride, the reaction velocity is decreased (Table 5). This behaviour may be interpreted in a similar manner to the salt effects for S_N1 reactions :

$$RCl + HgCl_2 \underset{\text{Fast}}{\overset{\text{Slow}}{\rightleftharpoons}} R^+ + HgCl_3^- \quad \ldots \quad (1)$$

$$R^+ + H_2O \xrightarrow[\text{Fast}]{} ROH \quad \ldots \quad (2)$$

$$HgCl_3^- \rightleftharpoons HgCl_2 + Cl^- \quad \ldots \quad (3)$$

The formation of the carbonium-ion is the slow rate-determining stage, the back-reaction being much faster and comparable with the formation of the product by reaction (2). Addition of chloride ions suppresses the dissociation of the mercuric complex ion, and the bimolecular back reaction between R^+ and $HgCl_3^-$ would therefore gain in importance by comparison with reaction (2). It is not possible to study salt effects where the added salt has no common ion, *e.g.*, lithium bromide, because under these conditions exchange of the halogens predominates.

The acetyl-glycosyl 1-halides are therefore suitable compounds by which to compare

[15] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, p. 359.
[16] Bayles, Bentley, A. G. Evans, and Jones, *J.*, 1955, 206; *Research*, 1952, **5**, 535.
[17] Lindberg, *Acta Chem. Scand.*, 1947, **1**, 710.

the uncatalysed solvolysis, which is an established S_N1 reaction, with the formation of the carbonium ion catalysed by mercuric salt. The stereochemical form is identical in the two cases, with almost complete inversion of configuration accompanying replacement of the halogen group. Such a definite stereochemical result is not normally associated with an S_N1 mechanism and it is this which led Isbell and Frush [1] to suggest an S_N2 mechanism. Inversion of configuration is probable, however, because the 2-acetyl group hinders entry of the reactant molecule at position 1 on the side leading to retention of configuration. The direction of departure of the replaced halogen group would also contribute to this tendency.

Our experiments also provide a comparison, based on the effect of solvent variation, for the catalysed and the uncatalysed mechanism; the general behaviour is similar but there are particular differences. Brown and Hudson [18] studied the effect of variation of solvent on the thermodynamics of S_N1 reactions. They investigated the variation in activation energy E and rate constant k, with changes in the solvent composition for several chlorides, and compared the behaviour with established S_N1 reactions. Fig. 3 shows results they quote for *tert.*-butyl chloride in comparison with our results for the catalysed and uncatalysed solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-chloride. The three instances are characterised by the constancy of the activation energy at high water contents. Brown

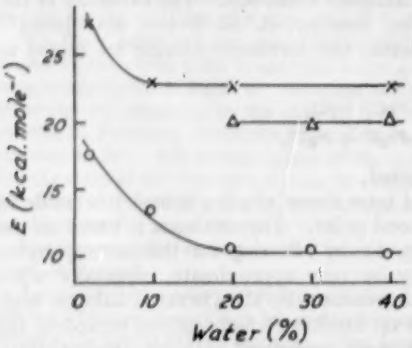


FIG. 3. *Variation of activation energy with solvent composition in acetone–water mixtures.*

× Bu^tCl.
△ Tetra-*O*-acetyl-α-D-glucosyl 1-chloride, uncatalysed.
○ Tetra-*O*-acetyl-α-D-glucosyl 1-chloride, catalysed.

and Hudson discussed the nature of the solvation process for the S_N1 reaction, where it is probable that the change in reaction velocity on increasing the polarity of the solvent is due entirely to variation in the entropy of activation, with little or no contribution from activation energy. Table 7 confirms this for the uncatalysed S_N1 solvolysis. When the proportion of water is increased, $\Delta S^\ddagger$ becomes less negative, but $\Delta H^\ddagger$ remains constant.

For the catalysed reaction the consequences of increasing the polarity of the solvent differ in some respects (Table 4). Increasing the proportion of water or methanol accelerates the rate of the reaction, but this is not so pronounced as for the S_N1 reaction (Table 7). For the catalysed reaction, varying the solvent from 80 to 60% acetone–water results in a three-fold increase in reaction rate, as compared with a ten-fold variation for the uncatalysed reaction. Nevertheless, the general variation in activation energy with solvent composition remains characteristic of the S_N1 process (Fig. 3), E becoming constant at high water or methanol concentrations. In reactions where Brown and Hudson [18] encountered S_N2 reactions, *e.g.*, the hydrolysis of *p*-nitrobenzoyl chloride in acetone–water, E showed a gradual increase with increasing solvent polarity, and this is no doubt related to the more diffuse charge distribution in the transition state of the bimolecular reaction. This difference in behaviour may thus be applied as a criterion for distinguishing between S_N1 and S_N2 reactions. The corresponding changes in entropy of activation with solvent composition for the catalysed reaction differ somewhat from those of the S_N1 reaction. As the solvent is varied from 2 to 20% of water in acetone, $\Delta S^\ddagger$ becomes much more negative. Further addition of water results in much smaller rate changes, giving almost constant values for

[18] Brown and Hudson, *J.*, 1953, 3352.

$\Delta S^{\ddagger}$. In methanol–acetone there is very little change in $\Delta S^{\ddagger}$ throughout the whole range of solvent variation. The large difference in activation energy between the uncatalysed and the catalysed reaction is noteworthy; the entropy factor is also less favourable in the latter.

The plot of log k_{25} against Y value of the solvent for the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-chloride in acetone–water is linear and consistent with an S_N1 reaction. The significance of these results will be discussed later.

There is a strong autocatalytic influence [6] of liberated hydrogen bromide during the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in methanol which is greater than in aqueous media. Salomaa [19] finds this behaviour a characteristic feature of 1-halogeno-ether solvolysis, and he observed that autocatalysis was more pronounced for solvents in which the liberated hydrogen halide is only slightly dissociated. He therefore regards the catalysis as arising from a positive salt effect rather than simple acid catalysis. Previously we [6] had also regarded this as a positive salt effect. Experiments where hydrogen bromide was added initially show that the initial rate is of the first order with respect to hydrogen bromide (Table 9). It appears therefore that hydrogen bromide functions as an electrophilic catalyst in a manner similar to the mercuric salts, giving rise to autocatalysis in non-solvolytic reactions: $RBr + HBr \longrightarrow R^+ + HBr_2^-$. This mechanism is supported by the evidence from the sugar halides and the 1-halogeno-ethers that un-ionised hydrogen halides are more effective catalysts than are ions formed in aqueous solution. The ions increase the reaction rate only in so far as they increase the polarity of the solvent and make conditions more conducive to the S_N1 reaction.

Experimental

Solvents.—Methanol and acetone were purified as described in earlier papers.

The term x% aqueous acetone refers throughout to a medium obtained by mixing at room temperature x volumes of dry solvent with $(100 - x)$ volumes of distilled water. Similarly x% methanol–acetone refers to a mixture of x volumes of methanol with $(100 - x)$ volumes of acetone.

Tetra-O-acetyl-α-D-glucosyl 1-Bromide.—This was prepared from β-penta-*O*-acetylglucose by treatment with hydrogen bromide in glacial acetic acid: the m. p. was 88—89°, and $[\alpha]_D^{20}$ +198° (*c*, 2·0 in $CHCl_3$).

Tetra-O-acetyl-α-D-glucosyl 1-Chloride.—This was prepared by treating β-penta-*O*-acetyl-glucose with titanium tetrachloride in chloroform and had m. p. 75—76°, $[\alpha]_D^{20}$ +166° (*c*, 2·1 in $CHCl_3$).

Reaction Product.—Tetra-*O*-acetyl-α-D-glucosyl 1-bromide (6 g.) and mercuric bromide (5·2 g.) were dissolved in methanol (250 ml.) and kept at 30°. After 24 hr. the solvent was removed under reduced pressure (at <50°) and the resulting mixture of syrup and mercuric bromide extracted with chloroform. The mercuric bromide was filtered off, the solution dried (Na_2SO_4), and the solvent removed under reduced pressure. The syrup crystallised only with great difficulty, giving methyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside, m. p. 103—105° (after 3 recrystallisations), $[\alpha]_D^{20}$ −17·5° (in $CHCl_3$).

Rate Measurements.—The solvolysis of the halide was followed in a 2·2 dm. polarimeter tube, fitted with a jacket through which water from a thermostat was circulated. The thermostat temperature was constant within ±0·1°.

(a) *Reactions catalysed by mercuric salts.* The experiments with tetra-*O*-acetyl-α-D-glucosyl 1-bromide were carried out at approx. room temperature. The mixture was prepared from a known quantity of the halide in acetone and a known quantity of mercuric salt dissolved in a suitable medium, and was transferred quickly to the polarimeter tube. The solutions were pre-heated to the reaction temperature in the thermostat.

Solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-chloride was studied from 50° to 100°, necessitating the use of a sealed-ampoule technique. The mixture was prepared at room temperature as above, heated in a thermostat at the required temperature for varying intervals in the ampoule, cooled in ice, and then transferred to the polarimeter tube for measurement.

The rate constants were evaluated from the initial rates of the reaction.

[19] Salomaa, "The Kinetics of 1-Halogenoether Alcoholysis," Annales Universitatis Turkuensis Turku, 1953.

(b) *Uncatalysed reactions.* For the tetra-*O*-acetyl-α-D-glucosyl 1-bromide the technique was that recorded in previous publications. For the chloride the sealed-ampoule technique was necessary.

Tables 10—12 show typical runs, only a part of the experimental observations being given. In general, the calculated values of the activation energy are accurate to ± 0·3 kcal.

TABLE 10. *Solvolysis of tetra-O-acetyl-α-D-glucosyl 1-bromide in 98% acetone–water at 25·2° catalysed by mercuric bromide.*

[RBr] = 0·05M. [$HgBr_2$] = 0·074M.

t (min.)	0	2	3	4	5	6	8	10	12	20	45	1200
α	7·59°	4·52°	3·46°	2·61°	2·41°	2·14°	1·72°	1·58°	1·34°	1·10°	1·50°	3·13°

$(d\alpha/dt)_{t=0}$ = 4·1 degree min.$^{-1}$. $k_1 = 1·2 \times 10^{-1}$ l. mole^{-1} sec.$^{-1}$.

TABLE 11. *Solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in 70% acetone–water at 100°.*

[RCl] = 0·05M.

t (min.)	0	4	8	12	16	41	71	101	175	265	600	660
α	6·34°	5·99°	5·69°	5·40°	5·10°	3·60°	2·93°	2·49°	1·74°	1·55°	1·23°	1·27°

$(d\alpha/dt)_{t=0} = 7·9 \times 10^{-2}$ degree min.$^{-1}$. $k_1 = 2·14 \times 10^{-4}$ sec.$^{-1}$.

TABLE 12. *Solvolysis of tetra-O-acetyl-α-D-glucosyl 1-chloride in absolute methanol at 25·2°, catalysed by mercuric chloride.*

[RCl] = 0·049M. [$HgCl_2$] = 0·067M.

t (hr.)	0·1	0·5	1·0	1·5	2·0	3·0	5·0	22	25	29	45	70	∞
α	6·42°	6·31°	6·23°	6·12°	6·04°	5·84°	5·43°	2·64°	2·10°	1·54°	0·35°	−0·13°	−0·38°

$(d\alpha/dt)_{t=0} = 3·25 \times 10^{-3}$ degree min.$^{-1}$. $k_2 = 1·14 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

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UNIVERSITY COLLEGE, CARDIFF. [*Received, December 12th*, 1955.]

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361. *Potential Radiosensitizers: Some Quinones and Related Compounds.*

By K. J. M. ANDREWS, D. H. MARRIAN, and D. R. MAXWELL.

Since some quinol bis(disodium phosphates) sensitize growing tissue towards the effects of ionizing radiation, three compounds of this type have been prepared bearing a radioactive atom for metabolic studies. The syntheses of some related compounds containing iodine are also included.

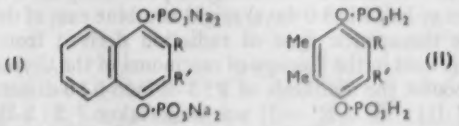
Bromination of the Diels–Alder adduct of toluquinone and butadiene leads to either a tri- or a tetra-bromo-derivative depending on conditions. The structure of each of these compounds has been determined.

FOR some years, work in these laboratories has been aimed at the synthesis of compounds which would sensitize growing tissue towards the curative or palliative effects of *X*-irradiation. Injections of cyanide or iodoacetic acid have been reported to sensitize tumour tissues to radiation,[1] and certain iodides,[2] gonadotropic hormone,[3] and fluorescein [4] seemed to have similar properties; investigation of the effect of oxygen tension [5] has led to the practice of oxygen inhalation by patients about to undergo *X*-ray therapy. Cornil

[1] Harker and Moppett, *Austral. J. Exp. Biol.*, 1936, **14**, 15.
[2] Ito, *Japan. J. Obstet. Gyn.*, 1937, **20**, 541.
[3] Narimatsu, *ibid.*, p. 411.
[4] Umanskii, Varshauskii, and Kudokobaev, *Doklady Akad. Nauk S.S.S.R.*, 1949, **65**, 581.
[5] See Hollaender, "Symposium on Radiobiology," Chapman and Hall Ltd., London, 1952, p. 285, for a review.

and Stohl [6] claimed that the radiosensitivity of a cell is related to its nucleic acid content and that the greater the ratio of deoxyribonucleic acid to ribonucleic acid, the higher the sensitivity.

Previous work from these laboratories [7] has shown that 2-methyl-1 : 4-naphthaquinol bis(disodium phosphate) (I; R = Me, R′ = H) inhibited mitosis of chick-heart fibroblast cultures (50% inhibition compared to controls by 4×10^{-6}M-solution), and, further, that the antimitotic and chromosome fragmentation effects of 150 r of 220-kv *X*-rays in conjunction with the phosphate (I; R = Me, R′ = H) (2×10^{-6}M) were much greater than the sum of the effects due to *twice* the dose of *X*-rays and *twice* the concentration of phosphate acting separately.[8a] The compound (I; R = R′ = H) had the highest order of antimitotic activity yet reported,[9] the concentration causing 50% inhibition being 3×10^{-9}M. Both the phosphates (I; R = R′ = H and Me) [10] were potent radiosensitizers.[8b] The halogenated derivatives (I; R = Me or H, R′ = Br) retained the property of mitotic inhibition.[11]



First stages of a clinical trial of the phosphate (I; R = Me, R′ = H) as an adjunct to *X*-ray therapy of inoperable carcinoma of the bronchus have been reported,[12] but the *small* clinical effect observed should not be allowed to diminish the important finding that such an effect as sensitization towards *X*-ray is possible and that, *in vitro*, the effect on growing tissues is reproducible and of an encouragingly high order.

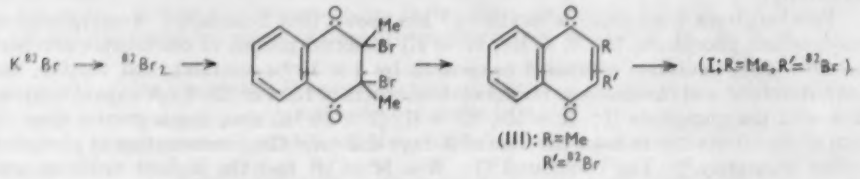
We visualize that an efficient radiosensitizing agent would have to fulfil certain criteria. It must increase those effects of *X*-rays on tissues which are important in the cure or palliation of malignant conditions, especially the effects on mitosis and on chromosome structure; it should be more effective on rapidly growing than on resting tissue; and it should be well tolerated by the patient. The second criterion could be met if the compound were to become concentrated selectively in growing tissue and in an attempt to study this possibility some potential radiosensitizers containing a labelled atom have been prepared.

The metabolism of the phosphate (I; R = Me, R′ = H) containing radio-phosphorus has been studied by Neukomm and his co-workers [13] but the interpretation of the results had to take into account very rapid enzymic dephosphorylation with the liberation of radioactive inorganic phosphate. Moreover, since Jaques, Millar, and Spinks [14] have shown that rats which had been injected with 2-[^{14}C]methyl-1 : 4-naphthaquinone excreted the corresponding quinol bis(disodium phosphate), labelling the compound with ^{32}P had serious drawbacks for metabolic studies. A more reliable indication of the metabolism of the salt (I; R = Me, R′ = H) would follow from a study of the distribution of the compound bearing ^{14}C in the 2-methyl group and starting with the corresponding quinone (made available to us by the generosity of Dr. Wright Langham, of the Los Alamos Scientific Laboratory), 2-[^{14}C]methyl-1 : 4-naphthaquinol bis(disodium phosphate) (I; R = $^{14}CH_3$, R′ = H) was prepared by conventional methods.

In another approach we sought to make use of ^{82}Br (an energetic γ-emitter) instead of the very weak β-emitter ^{14}C. 2-Bromo-3-methyl-1 : 4-naphthaquinol bis(dihydrogen

[6] Cornil and Stohl, *Presse Med.*, 1951, **59**, 933.
[7] Mitchell and Simon-Reuss, *Nature*, 1947, **160**, 98.
[8] *Idem*, *Brit. J. Cancer*, 1952, **6**, (*a*) 305; (*b*) 317.
[9] Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, 1948, **3**, 263.
[10] Marrian, *J.*, 1954, 760.
[11] Friedmann, Marrian, and Simon-Reuss, *Biochim. Biophys. Acta*, 1952, **8**, 680.
[12] Mitchell, *Brit. J. Cancer*, 1953, **7**, 313.
[13] Neukomm, Peguiron, Lerch, and Richard, *Arch. internat. Pharmacodyn. Therapie*, 1953, **93**, 373; Neukomm, Radiobiology Symposium, Butterworths Scientific Publns., London, 1954, p. 189.
[14] Jaques, Millar, and Spinks, *Schweiz. Med. Woch.*, 1954, **29**, 792.

phosphate) had already been prepared,[11] and this synthesis was modified for the preparation of the corresponding compound containing ^{82}Br as follows :



Studies of the metabolism of the phosphates (I; R = $^{14}CH_3$, R′ = H) and (I; R = Me, R′ = ^{82}Br) have been briefly reported.[15] ^{82}Br, a γ-emitter, has the disadvantage of a short half-life (35 hours) and ^{14}C the disadvantages associated with low-energy β-emission (0·156 mev) and it was felt that the labelling of potentially interesting compounds with ^{131}I (a β- and γ-emitter of half-life 8·0 days) might combine ease of detection and estimation with even a possible therapeutic dose of radiation derived from the compound itself (cf. ^{131}I-iodide which is used in the therapy of carcinoma of the thyroid gland).

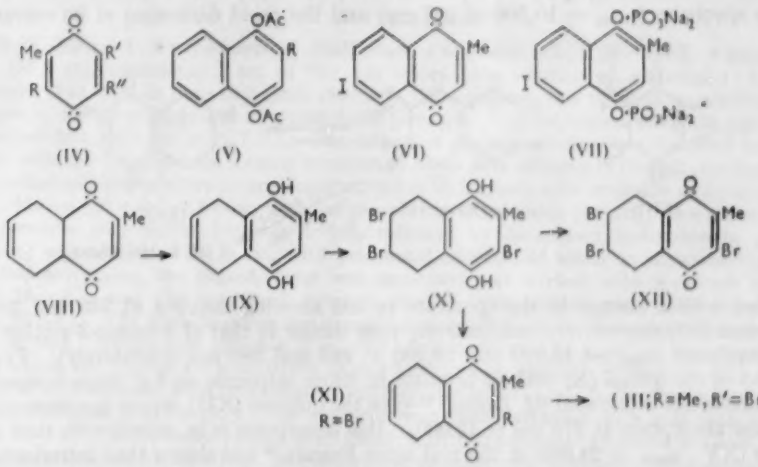
As a model compound the synthesis of 2 : 3-di-iodo-5 : 6-dimethylbenzoquinol bis(dihydrogen phosphate) (II; R = R′ = I) was undertaken. 2 : 3-Dibromo-5 : 6-dimethylbenzoquinone reacted readily with sodium iodide in boiling ethyl methyl ketone, to give the dark red di-iodo-quinone which was reduced to the quinol and phosphorylated. A satisfactory yield of the phosphate (II; R = R′ = I) resulted. When the synthesis was undertaken with sodium ^{131}I-iodide, the need to conserve radioactivity suggested that only the theoretical amount of sodium iodide should be used. This resulted in an even better yield of crystalline di-iodo-quinone but the lower melting point and analytical figures indicated contamination with about 3% of the starting dibromo-quinone. This was felt to be unimportant, especially as reduction and phosphorylation still gave an excellent yield of the phosphate (II; R = R′ = ^{131}I). Contamination was again evident from the analytical figures and this was confirmed by paper chromatography. Autoradiography of the paper strip showed that more than 95% of the radioactivity of the sample was associated with the main component, that traces were present in material behaving like the corresponding quinone, but that none was present as iodide ion.

This synthesis suggested that bromine atoms attached to the quinone ring could be replaced by iodine provided that the oxidation–reduction potential of the quinone–quinol was lower than that of the iodide–iodine system. This condition was not fulfilled by 5-bromo- or 5-chloro-toluquinone (IV; R = R′ = H, R″ = Br or Cl), by tribromotoluquinone (IV; R = R′ = R″ = Br), or by 5-bromo-2 : 3-dimethyl-1 : 4-benzoquinone (IV; R = Me, R′ = H, R″ = Br), all of which liberated iodine when treated with sodium iodide in acetone.

Preliminary metabolic experiments with the phosphates (I; R = Me, R′ = ^{82}Br) and (II; R = R′ = ^{131}I) showed that the halogen attached to the quinol ring was rapidly liberated as halide ion.[15] Simple ion interchange between the bromo-quinone (III; R = Me, R′ = Br) and salts contained in the body was unlikely to account for this since attempts to prepare the iodo-quinone (III; R = Me, R′ = I) by an exchange reaction between 2-bromo-3-methyl-1 : 4-naphthaquinone (III; R = Me, R′ = Br) and iodide ion were not successful. A possible mechanism for liberation of halide ion *in vivo* involves enzymic dephosphorylation to the quinol which would immediately equilibrate with the corresponding quinone. The halogenated quinone (III; R = Me, R′ = Br) or (IV; R = Me, R′ = R″ = I) might then be attacked by thiol-containing material with elimination of halide ion. 2-Chloro- and 2 : 3-dichloro-1 : 4-naphthaquinones (III; R = Cl, R′ = H; and R = R′ = Cl) react with thiols in this way,[16] and so does chloranil,[17] and it was found

[15] Maxwell, "Second Radioisotopes Conference, 1954," Butterworths Scientific Publns., London, 1954, Vol. I, p. 200.
[16] Fieser and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3609.
[17] Schubert, *ibid.*, 1947, **69**, 712.

that the quinone (III; R = Me, R′ = Br) reacted smoothly with sodium mercaptoacetate to give the acid (III; R = Me, R′ = S·CH_2·CO_2H) identical with a specimen prepared from 2-methyl-1 : 4-naphthaquinone and mercaptoacetic acid.[18] The quinone (IV; R = Me, R′ = R″ = I) also reacted with sodium mercaptoacetate to give the quinone-acid (IV; R = Me, R′ = R″ = S·CH_2·CO_2H), isolated and purified as the derived quinol. The lability of bromine in compounds analagous to (I; R = Me, R′ = Br) was also observed by Carrava [19] who showed that 2-bromo-3-methyl-1 : 4-naphthaquinol suffered quantitative loss of bromide under alkaline conditions.



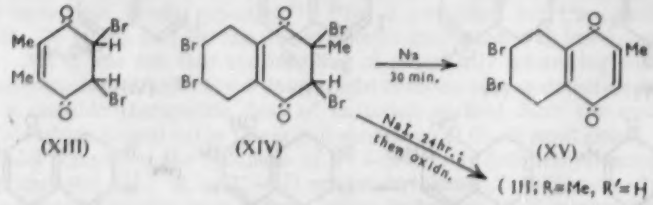
This ready loss of halogen from the phosphates (I; R = Me, R′ = Br) and (II; R = R′ = I) made compounds such as (III; R = CH_2Br, R′ = H) and (V; R = CH_2Br or CH_2I) of little interest as intermediates, but 2-bromomethyl-1 : 4-naphthaquinone (III; R = CH_2Br, R′ = H) was readily obtained by Ziegler bromination of 2-methyl-1 : 4-naphthaquinone in hot acetic anhydride in the presence of dibenzoyl peroxide, and the quinol diacetate (V; R = CH_2Br) from 1 : 4-diacetoxy-2-methylnaphthalene and *N*-bromosuccinimide in carbon tetrachloride. Both compounds decomposed on storage, but the quinol diacetate reacted smoothly with sodium iodide to give 1 : 4-diacetoxy-2-iodomethylnaphthalene (V; R = CH_2I) which was also unstable. No attempts were therefore made to convert these compounds into the corresponding bis(dihydrogen phosphates).

Halogenation of the quinol ring having proved unsatisfactory, attention was turned to the introduction of halogen into the benzenoid ring. Thus 6-methyl-2-naphthylamine was converted in turn into the 2-iodo-compound, the iodo-quinone (VI), and the bis(disodium phosphate) (VII). However, the early introduction of the iodine atom into the molecule and the low overall yield of (VII) rendered this synthesis of little value for the preparation of a therapeutic agent containing ^{131}I. Attempts to prepare the compound (VI) or (VII) labelled with ^{131}I by exchange reactions between the inactive compounds and ^{131}I-iodine were unsuccessful. Similar failures to prepare iodine-labelled derivatives of 2-methyl-1 : 4-naphthaquinone or the corresponding quinol bis(disodium phosphate) were encountered.

It seemed possible that Diels–Alder adducts between toluquinone and butadiene might be convenient starting materials for the preparation of similar compounds and, although iodo-compounds were not obtained, some interesting observations have been recorded. The adduct (VIII) [20] was isomerised to the quinol (IX) by a trace of hydrobromic acid in hot acetic acid. When this was treated in ether suspension with 3 mols. of bromine in

[18] Fieser and Turner, *J. Amer. Chem. Soc.*, 1947, **69**, 2335.
[19] Carrava, *Gazzetta*, 1943, **73**, 225, 237, 238.

acetic acid, a tribromide (X) crystallised on cooling, the structure of which has been deduced as follows. Its analyses indicated a formula $C_{11}H_{11}O_2Br_3$, and it was soluble in alkali and absorbed ultraviolet light maximally at 290 mμ (ε 4200). This wavelength is close to the maximum absorption of quinol (ε 2970 at 294 mμ) and the naphthaquinol (IX) (ε 3600 at 290 mμ). Treatment of the tribromide (X) with sodium iodide in acetone, followed by gentle oxidation, gave the unstable quinone (XI; R = Br) (cf. Finkelstein [21]). Vigorous oxidation of this by chromic acid in acetic acid [22] gave 2-bromo-3-methyl-1 : 4-naphthaquinone (III; R = Me, R′ = Br) which was identified by comparison with an authentic specimen.[23] The freshly prepared quinone (XI; R = Br) had a typical bromobenzoquinone spectrum ($\varepsilon_{max.}$ = 10,500 at 267 mμ) and the rapid darkening of its colour was



associated with a change in the spectrum to one showing maxima at 245 and 280 mμ (ε 7300 and 7900 respectively) qualitatively very similar to that of 2-bromo-3-methyl-1 : 4-naphthaquinone ($\varepsilon_{max.}$ = 13,700 and 13,200 at 245 and 280 mμ respectively). Further, oxidation of the quinol (X) with dichromate in dilute sulphuric acid at room temperature or bromine in hot acetic acid (cf. Zincke) [24] gave the quinone (XII), whose spectrum showed maximum absorption at 275 mμ (ε 12,900); this absorption is in accord with that of the quinone (XV; $\varepsilon_{max.}$ = 24,000 at 255 mμ) since Braude [25] has shown that introduction of bromine into a quinone ring tends to decrease the extinction coefficient by about 50% and to increase the wavelength of maximal absorption by 10—20 mμ. The residual bromine atom in the quinone (XI; R = Br) appeared unreactive towards iodide ion, a behaviour also shown by the analogue (III; R = Me, R′ = Br).

More vigorous bromination of the quinol (IX) in hot acetic acid gave a colourless compound $C_{11}H_{10}O_2Br_4$, insoluble in alkali and unaffected by mild oxidation. This is considered to be (XIV) on the grounds of its analytical composition, its lack of colour, and its maximal absorption of ultraviolet light at 275 mμ (ε 5300) which accords well with the properties of a similar type of compound, 2 : 3-dibromo-2 : 3-dihydro-5 : 6-dimethyl-1 : 4-benzoquinone (XIII) ($\varepsilon_{max.}$ = 8300 at 275 mμ) obtained by addition of 1 mol. of bromine to 2 : 3-dimethyl-1 : 4-benzoquinone. Moreover, treatment of the compound (XIV) with sodium iodide again eliminated two bromine atoms to give the quinone (XV) (cf. Zincke [26] who prepared 2 : 3-dichloro-1 : 4-naphthaquinone by action of potassium iodide on the corresponding dihydronaphthaquinone tetrachloride). The quinone (XV), when first prepared, had a typical quinone spectrum ($\varepsilon_{max.}$ 25,000 at 255—256 mμ) but on storage the compound changed to a mixture of indefinite melting point and became only partially soluble in alcohol. These changes were not associated with the pronounced darkening shown by the compound (XI; R = Br) but recall the dimerisation of 2-methyl-1 : 4-naphthaquinone in sunlight. More prolonged treatment of the tetrabromo-compound (XIV) with sodium iodide eliminated all four bromine atoms. The resulting compound, which rapidly changed colour from yellow to purple in air and was doubtless 5 : 8-dihydro-2-methyl-1 : 4-naphthaquinone (XI; R = H) gave 2-methyl-1 : 4-naphthaquinone (III;

[20] Fieser and Chang, *J. Amer. Chem. Soc.*, 1942, **64**, 2043.
[21] Finkelstein, *Ber.*, 1910, **43**, 1530.
[22] Fieser, Campbell, and Fry, *J. Amer. Chem. Soc.*, 1939, **61**, 2206.
[23] Adams, Giessmann, Baker, and Teeter, *ibid.*, 1941, **63**, 533.
[24] Zincke, *Ber.*, 1887, **20**, 1777.
[25] Braude, *J.*, 1945, 490.
[26] Zincke, *Annalen*, 1889, **255**, 356, 369.

R = Me, R′ = H) on oxidation with chromic acid. These reactions and properties complete the identification of 2 : 3 : 6 : 7-tetrabromo-2 : 3 : 5 : 6 : 7 : 8-hexahydro-2-methyl-1 : 4-naphthaquinone (XIV).

Under the usual conditions, the quinol (IX) readily formed a bis(dihydrogen phosphate), isolated as its tetra*cyclo*hexylamine salt. Treatment of an aqueous solution of the latter with excess of sulphuric acid caused the mono*cyclo*hexylamine salt to crystallise—a derivative apparently less sensitive to light than the original salt.

Experimental

2-[^{14}C]*Methyl*-1 : 4-*naphthaquinol Bis*(*barium Phosphate*).—2-[^{14}C]Methyl-1 : 4-naphthaquinone (57·8 mg. containing 1 mc of ^{14}C) was added to a solution of 2-methyl-1 : 4-naphthaquinone (940 mg.) in pure dry ether (60 c.c.). The quinone was reduced by shaking it with platinum oxide and hydrogen at atmospheric pressure. Uptake ceased when 131 c.c. had been absorbed (req., 131 c.c. at N.T.P.). The colourless ethereal solution was decanted into a flask filled with nitrogen, and the solvent removed *in vacuo* over nitrogen. Dimethylaniline (12 c.c.) was added and the mixture magnetically stirred in an ice-bath with exclusion of moisture during the addition (30 min.) of freshly distilled phosphorus oxychloride (10 c.c.), then stirred at room temperature over-night. Ice was added, followed by 5N-sodium hydroxide to pH 8—9. Stirring was continued for 3 hr., with occasional addition of alkali to maintain the slightly alkaline conditions, the organic layer was separated and washed with N-sodium hydroxide (2 × 10 c.c.), and the combined aqueous phases were washed with methylene chloride (2 × 20 c.c.). The aqueous phase was brought to neutrality by addition of concentrated hydrochloric acid. Ammonium chloride (6 g.) and calcium chloride (6 g. of the hexahydrate) were then added, the precipitate was filtered off and washed with water (5 × 10 c.c.). The combined filtrates were acidified with concentrated hydrochloric acid (12 c.c.) with stirring and extracted with butan-1-ol (4 × 20 c.c.). The extracts were then extracted with N-sodium hydroxide (4 × 20 c.c.), the aqueous phases neutralised with concentrated hydrochloric acid, and the volume reduced to about 40 c.c. by evaporation *in vacuo* over nitrogen. Ammonium chloride (2·0 g.) and barium chloride (3·5 g. of dihydrate) were then added, and the solution was clarified by filtration through Hyflo and boiled. The *barium salt* crystallized (reverse solubility); the yield was 1·5 g. (38%) after a further recrystallization from water (Found, in material dried *in vacuo* at room temperature: C, 19·7; H, 2·9; P, 9·05. $C_{11}H_8O_8P_2Ba_2,4\frac{1}{2}H_2O$ requires C, 19·3; H, 2·5; P, 9·0%). Ultraviolet max. at 226 (ε 45,500) and 290 mμ (ε 5600) in 0·01N-HCl.

A solution of the sodium salt was obtained by ion-exchange over Dowex 50 (Na form). The radioactive and chemical purity of such a solution was tested by paper chromatography (descending) on Whatman No. 1 in saturated ammonium sulphate (80 vol.), M-sodium acetate (20 vol.) and *iso*propyl alcohol (2 vol.). Located by the photographic technique described by Markham and Smith [37] (except that an unfiltered mercury discharge tube was used as the light source), the main spot had R_F 0·55 and was contaminated by traces of material remaining near the origin. More than 99% of the radioactivity of the solution was associated with the main spot, the rest being associated with the slow-moving material. The specific activity of the material was shown to be 0·44 μc/mg. of the tetrasodium salt compared to the calculated value of 0·41 μc/mg.

2-[^{82}Br]*Bromo*-3-*methyl*-1 : 4-*naphthaquinone*.—All reactions involving ^{82}Br were carried out in a well-ventilated hood behind 2 inches of lead. The initial oxidation of potassium bromide to bromine is an adaptation of the method described by Twombly and Schoenewaldt.[38]

Potassium [^{82}Br]bromide (1·4 g. containing 250 mc of ^{82}Br) was dissolved in water (10 c.c.) in a 100 c.c. flask fitted with dropping funnel and gas-inlet and -exit tubes. The gas inlet was branched to the top of the dropping funnel to avoid pressure differences. The contents of the flask were warmed to 40° and stirred during the slow addition of a solution of manganese dioxide (2·0 g.) in concentrated sulphuric acid (20 c.c.) from the funnel. The liberated bromine was transferred by a slow stream of nitrogen through a sulphuric acid drying-tube into a 100 c.c. flask containing 2-methyl-1 : 4-naphthaquinone (1·0 g.), anhydrous sodium acetate (2·0 g.), and acetic acid (15 c.c.), the whole being immersed in liquid air. The exit tube from this flask led through a safety tube to two gas traps containing acetic acid. After final addition of the

[37] Markham and Smith, *Biochem. J.*, 1949, **45**, 294.
[38] Twombly and Schoenewaldt, *Cancer*, 1950, **3**, 601.

oxidizing mixture, liberation of bromine was completed by warming to 70°. When all the bromine had been transferred, the reaction flask was removed from the liquid-air bath, disconnected from the rest of the apparatus, and fitted with an efficient reflux condenser and soda-lime tube. As the bromine melted, acetic acid (5 c.c.) was added and the whole warmed to 50° in a water-bath. After 3 hr., the contents of the flask were cooled and water added to precipitate the quinone, which was filtered off in a tall, cylindrical, sintered-glass funnel. The above technique is adapted from the published method.[10]

2-[^{82}Br]*Bromo-3-methyl*-1 : 4-*naphthaquinol Bis*(*disodium Phosphate*).—A rubber teat was placed over the stem of the filter funnel containing the quinone described above, and dry ether (70—80 c.c.) added. Anhydrous calcium sulphate was added (20 g.), the ethereal solution dried by gentle stirring, the rubber teat removed, and the solution allowed to filter into a dry flask (100 c.c. capacity). Reduction to the quinol and subsequent phosphorylation were carried out as described for the ^{14}C-compound above, except that the phosphorus oxychloride was diluted with an equal volume of dry toluene before addition. Before hydrolysis next day, solvents were removed by distillation *in vacuo* over nitrogen, and the residue was treated with ice and alkali as described. Extractions into and out of butanol were carried out by mechanical stirring in the separating funnel to avoid handling. The final alkaline extracts, evaporated to half bulk, were treated with alcohol to turbidity, and the whole was chilled overnight. Colourless hydrated needles of the *bis*(*disodium phosphate*) resulted (yield 34%) (Found, in material dried *in vacuo* at room temperature: C, 21·0; H, 3·2; P, 9·4. $C_{11}H_7O_8P_2BrNa_4,7H_2O$ requires C, 21·0; H, 3·4; P, 9·9%). Ultraviolet max. at 232 (ε 70,000) and 290 mμ (ε 5800) in 0·01N-HCl. These figures agree with those obtained from a specimen of the free acid corresponding to the above salt which had been prepared previously.[11] The material moved as a single spot in the solvent system described above (R_F 0·39) and more than 95% of the radioactivity of the sample was shown to be associated with this spot (measured by autoradiography of the paper strip on Ilford *X*-ray film).

2 : 3-*Di-iodo*-5 : 6-*dimethyl*-1 : 4-*benzoquinone*.—2 : 3-Dibromo-5 : 6-dimethyl-1 : 4-benzoquinone (5·0 g.) and sodium iodide (7 g.) were gently refluxed overnight in ethyl methyl ketone (125 c.c.; redistilled). The solvent was evaporated *in vacuo*, and the residue suspended in acetone and poured into water. The red-brown crystals were filtered off, washed with water, and recrystallized from hot alcohol (yield, 3·0 g., 45·5%; m. p. 157—158°).

For analysis, the *compound* was recrystallized twice more from alcohol and formed dark red needles, m. p. 159·5—160° (Found, after drying *in vacuo* at room temperature for 2 hr.: C, 25·0; H, 1·6; I, 66·4. $C_8H_6O_2I_2$ requires C, 24·8; H, 1·6; I, 65·4%). The same reaction, carried out with the dibromoquinone (1·0 g.) and sodium iodide (1·0 g.), gave (after recrystallization from alcohol) 0·83 g. (62%) of red prisms, m. p. 148—149°. This material contained 3·0% of bromine, presumably as unchanged dibromoquinone. This was the scale on which the reaction with sodium [^{131}I]iodide was carried out.

2 : 3-*Di-iodo*-5 : 6-*dimethyl*-1 : 4-*benzoquinol Bis*(*dihydrogen Phosphate*).—The above di-iodoquinone (3·5 g.) was reduced in ether by shaking it with aqueous sodium dithionite and the washed and dried quinol phosphorylated as described above for the [^{82}Br]bromo-compound. The mixture was evaporated *in vacuo* at 100° and the resulting gum dissolved in methylene chloride, treated with ice, and brought to pH 8—9 by adding aqueous sodium hydroxide to the stirred mixture. During 3 hr., further additions of alkali kept the solution just alkaline to phenolphthalein. A solution of barium chloride (20 g.) in water was next added, the precipitate separated at the centrifuge, and an equal volume of alcohol added to the supernatant liquid. The precipitated bis(barium phosphate) was collected (centrifuge), washed, and dried (4·9 g., 66%). This salt (3·9 g.) was converted into the acid by percolation through a column of Dowex 50 (H^+ form), and the eluate evaporated to small bulk *in vacuo* over nitrogen. The *compound* separated in colourless prisms, m. p. 242° (decomp.) (600 mg., 52%). After one recrystallization from hot water, it had m. p. 242·5° (decomp.) (Found, in material dried *in vacuo* at room temperature for 2 hr.: C, 17·9; H, 1·8; I, 46·2. $C_8H_{10}O_8P_2I_2$ requires C, 17·5; H, 1·8; I, 46·2%). Repetition of this preparation with the slightly impure radioactive di-iodoquinone gave the labelled compound in similar yield.

5-*Bromotoluquinone*.—Toluquinone (1·0 g.; steam-distilled) was treated in acetic acid (5 c.c.) with bromine (0·45 c.c.) in acetic acid (5 c.c.). Anhydrous sodium acetate (1·0 g.) was added immediately, and the whole warmed till reaction began and left on the steam-bath for 5 min. The solution was poured into water and stirred till the precipitate solidified, and the solid recrystallized from alcohol. The *compound* formed yellow prisms (350 mg., 23%), m. p. 99—100° after softening. For analysis, one recrystallization from hexane raised the m. p. to

105—107° (Found, in material dried *in vacuo* at room temperature, under which conditions the compound is volatile: C, 42·0; H, 2·5; Br, 39·6. $C_7H_5O_2Br$ requires C, 41·8; H, 2·5; Br, 39·75%). The compound is also easily prepared as follows. Toluquinone (1·0 g.) in acetic acid (5 c.c.) was treated with hydrobromic acid in acetic acid (2 c.c.; 50% w/v) with shaking. The colour was quickly discharged, at which point a solution of potassium dichromate (5 g.) and sulphuric acid (2 c.c.) in water (50 c.c.) was added. The resulting solution was chilled in ice, and the crystalline solid filtered off, and washed well with water and then with alcohol (yield, 1·1 g., 67%; m. p. 103—105°).

5-Chlorotoluquinone.—The method reported by Cason, Allen, and Goodwin [29] appeared unnecessarily cumbersome so the compound was prepared as follows: toluquinone (5·0 g.) in acetic acid (25 c.c.) was stirred and treated dropwise with concentrated hydrochloric acid (15 c.c.). 5-Chlorotoluquinol crystallized and was dissolved by warming. Potassium dichromate (25 g.) and sulphuric acid (10 c.c.) in water (250 c.c.) were next added and the whole allowed to cool. 5-Chlorotoluquinone crystallized in 66% yield (m. p. 105—106·5°; Cason *et al.*[29] give 103—104°).

3 : 5 : 6-Tribromotoluquinone.—The conditions described above for the first preparation of 5-bromotoluquinone were repeated, but with twice as much bromine and sodium acetate. Worked up as before, the compound formed yellow prisms (30%), m. p. 233° (decomp.) after two recrystallizations from alcohol followed by sublimation at 140—160°/1 mm. (Found, in material dried *in vacuo* at 50°: C, 23·0; H, 0·9; Br, 66·8. Calc. for $C_7H_2O_2Br_3$: C, 23·4; H, 0·8; Br, 66·8%). Fichter and Rinderspacher [30] give m. p. 234°.

2 : 3-Dibromo-2 : 3-dihydro-5 : 6-dimethyl-1 : 4-benzoquinone.—2 : 3-Dimethyl-1 : 4-benzoquinone (1·0 g.) in acetic acid (5 c.c.) was warmed with bromine (1·2 g.) in acetic acid (5 c.c.). When the colour had been discharged, the solution was poured into water, and the pale yellow prisms were filtered off, washed with water, and dried in air (yield 1·75 g., 80%; m. p. 100—102°). After two sublimations *in vacuo* and one recrystallization from hexane, the *compound* had m. p. 104—105° (Found, in material dried *in vacuo* at room temperature: C, 32·6; H, 2·9; Br, 53·7. $C_8H_8O_2Br_2$ requires C, 32·4; H, 2·7; Br, 54·0%). Ultraviolet max. at 275 mμ (ε 8300).

5-Bromo-2 : 3-dimethyl-1 : 4-benzoquinone.—The above dibromo-compound (1·7 g.) was shaken overnight with a solution of anhydrous sodium acetate (1·0 g.) in acetic acid (10 c.c.). The whole was poured into water and scratched. The *product* formed orange prisms (600 mg., 49%), m. p. 42—43° not raised by recrystallization from alcohol (Found, in material dried *in vacuo* at room temperature: C, 45·0; H, 3·9; Br, 37·55. $C_8H_7O_2Br$ requires C, 44·5; H, 3·7; Br, 37·0%).

2-Carboxymethylthio-3-methyl-1 : 4-naphthaquinone.—Conditions described by Fieser and Turner [18] were followed except that 2-bromo-3-methyl-1 : 4-naphthaquinone was used as starting material. The compound was isolated in 49% yield with m. p. 156—159° raised to 159—161° by recrystallization from benzene. The m. p. was not depressed on admixture with an authentic specimen.

2 : 3-Dicarboxymethylthio-5 : 6-dimethyl-1 : 4-benzoquinol.—Mercaptoacetic acid (0·62 c.c.; redistilled) was neutralized with sodium hydroxide and slowly added to a solution of 2 : 3-diiodo-5 : 6-dimethyl-1 : 4-benzoquinone (1·24 g.) in alcohol (10 c.c.). The mixture was refluxed for 1½ hr., the solvent distilled off *in vacuo*, and the dark residue taken up in a mixture of aqueous sodium dithionite and ether. The ether layer was removed, the aqueous phase was extracted 4 times with ether, and the extracts were combined with the original ether phase. The combined extracts were shaken with M-sodium carbonate (4 × 10 c.c.), and the alkaline extracts brought to pH 3—4 by addition of acetic acid and concentrated hydrochloric acid. This solution was extracted 4 times with ether, and the extracts were dried, boiled with charcoal, and filtered. Evaporation left a red solid which was recrystallized from 50% alcohol containing a little dithionite. High-melting, colourless prisms of *2 : 3-dicarboxymethylthio-5 : 6-dimethyl-1 : 4-benzoquinol* were deposited on cooling (0·6 g., 59%), which were recrystallized once more before analysis (Found: C, 45·8; H, 4·4; S, 20·0. $C_{12}H_{14}O_6S_2$ requires C, 45·3; H, 4·4; S, 20·1%).

2-Bromomethyl-1 : 4-naphthaquinone.—2-Methyl-1 : 4-naphthaquinone (1·0 g.), *N*-bromosuccinimide (1·0 g.), and dibenzoyl peroxide (15 mg.) were suspended in acetic anhydride (7·5 c.c.) and heated and shaken at 135° for a few minutes. When the colour lightened, the solution was poured on ice, and the liquid decanted. The yellow solid was triturated with alcohol and recrystallized from alcohol (5 c.c.) (yield, 360 mg., 27·5%). After recrystallization from methyl

[29] Cason, Allen, and Goodwin, *J. Org. Chem.*, 1948, **13**, 403.
[30] Fichter and Rinderspacher, *Helv. Chim. Acta*, 1927, **10**, 40.

alcohol, the *compound* formed yellow needles, m. p. 96° (decomp.) (Found, in material dried *in vacuo* at room temperature: C, 52·3; H, 2·8; Br, 30·3. $C_{11}H_7O_3Br$ requires C, 52·6; H, 2·8; Br, 31·8%). It decomposes when kept.

1 : 4-*Diacetoxy-2-bromomethylnaphthalene.*—1 : 4-Diacetoxy-2-methylnaphthalene[21] (8·0 g.), *N*-bromosuccinimide (5·6 g.), and dibenzoyl peroxide (*ca.* 100 mg.) were refluxed in carbon tetrachloride (15 c.c.) for 30 min. under a 200 w lamp. After this time, no active bromine remained in solution. More carbon tetrachloride (15 c.c.) was added, and the whole refluxed and filtered. The yellow prisms deposited on cooling were filtered off, washed, ground with water, filtered off, and dried in air (yield, 6·3 g., 61%; m. p. 138—141·5°). After two recrystallizations from methyl alcohol, the *compound* formed colourless prisms, m. p. 145—146° (Found, in material dried *in vacuo* at 50°: C, 53·5; H, 4·2; Br, 23·8. $C_{15}H_{13}O_4Br$ requires C, 53·4; H, 3·9; Br, 23·7%).

1 : 4-*Diacetoxy-2-iodomethylnaphthalene.*—1 : 4-Diacetoxy-2-bromomethylnaphthalene (6·0 g.) was refluxed for 1 hr. with sodium iodide in acetone (60 c.c. of 15% w/v). About half of the acetone was distilled off and the residue poured into water (200 c.c.). The precipitate was filtered off, washed with water, and dried *in vacuo* (yield, 6·7 g., 97%). After recrystallization from alcohol, there were obtained 4·45 g. (64%) of 1 : 4-*diacetoxy-2-iodomethylnaphthalene* as pale yellow prisms, m. p. 122—123° (decomp.). For analysis, the compound was recrystallized twice more from alcohol after which it formed almost colourless matted needles, m. p. 125·5° (decomp.) (Found, in material dried *in vacuo* at room temperature: C, 47·1; H, 3·5; I, 33·4. $C_{15}H_{13}O_4I$ requires C, 46·9; H, 3·4; I, 33·0%). The compound decomposes when kept.

2-*Iodo-6-methylnaphthalene.*—6-Methyl-2-naphthylamine (7·85 g.) was stirred in dilute sulphuric acid (5·6 c.c. of acid in 78 c.c. of water) at 5°. Sodium nitrite (5 g.) in water was added during *ca.* 30 min. Then urea was added, followed by a concentrated solution of potassium iodide (11·2 g.) in water. The mixture was left at room temperature for 1 hr., heated at 90° for 1 hr., and then left at room temperature overnight. The precipitate was removed, was washed with water, and dissolved in ether, and the solution was treated twice with charcoal. The filtered ethereal solution was evaporated and the residue recrystallized from light petroleum (b. p. 100—120°) (yield, 5·5 g., 42%). Recrystallization gave the *compound* as colourless prisms, m. p. 146—147° (Found: C, 48·9; H, 3·3; I, 47·9. $C_{11}H_9I$ requires C, 49·3; H, 3·4; I, 47·3%).

6-*Iodo-2-methyl*-1 : 4-*naphthaquinone.*—2-Iodo-6-methylnaphthalene (2·68 g.) was powdered and treated in acetic acid (15 c.c.) with chromium trioxide (5 g.) in water (3·5 c.c.) and acetic acid (3·5 c.c.), dropwise at <40°. The mixture was left at room temperature for 1 hr. and then warmed on a water-bath for 30 min. On cooling, most of the *quinone* crystallized, the remainder being obtained by dilution with water. It was washed with water. Recrystallization from methanol gave 1·1 g. (37%) of yellow needles, m. p. 136—137° (Found: C, 43·7; H, 2·4; I, 43·05. $C_{11}H_7O_2I$ requires C, 44·32; H, 2·37; I, 42·6%).

The identity was proved by oxidation with potassium permanganate which gave 4-iodophthalic acid, m. p. 182° (Found: C, 32·2; H, 2·1; I, 42·6. Calc. for $C_8H_5O_4I,\frac{1}{2}H_2O$: C, 31·9; H, 2·0; I, 42·2%).

6-*Iodo-2-methyl*-1 : 4-*naphthaquinol.*—6-Iodo-2-methyl-1 : 4-naphthaquinone (2·6 g.) was shaken in ether with aqueous sodium dithionite until colourless. The ethereal solution was dried (Na_2SO_4) and evaporated. The residue was twice dissolved in dry toluene and evaporated *in vacuo*, and then immediately used as follows:

6-*Iodo-2-methyl*-1 : 4-*naphthaquinol Bis*(*disodium Phosphate*).—Dry toluene (10 c.c.) and dimethylaniline (8 c.c.) were added to the above quinol, and the mixture cooled in ice and stirred under nitrogen. Phosphorylation and subsequent isolation of the barium salt closely followed the methods given for the radioactive phosphates described above. All the dibarium salt (2·16 g.) was suspended in water (10 c.c.) and stirred and cooled in ice. Barium ions were removed by sodium sulphate, and the filtrate evaporated *in vacuo* below 40° to small volume. Addition of alcohol gave a white precipitate which was filtered off and dried (1·1 g.). The *compound* recrystallized from methanol–ethanol as colourless needles (0·8 g.) which, although hygroscopic, resolidified in air (Found, in material dried *in vacuo* at 110°: C, 24·5; H, 1·6; P, 11·0; I, 22·2. $C_{11}H_7O_6P_2INa_4$ requires C, 24·1; H, 1·3; P, 11·3; I, 23·2%). Ultraviolet max. at 229 (ε 34,580), 247 (ε 38,050), and 288—292 mμ (ε 5740).

The compound gave one ultraviolet-absorbing spot, with a small cap, on a paper chromatogram [ascending in butan-1-ol (50 vol.), acetic acid (15 vol.), and water (35 vol.) for 17 hr.] (R_F 0·45—0·5)

[21] Anderson and Newman, *J. Biol. Chem.*, 1933, **103**, 405.

Attempted Exchange Reactions with 6-Iodo-2-methyl-1 : 4-naphthaquinone and the Corresponding Quinol Bis(disodium Phosphate).—(*a*) The quinone (4 mg.) in butan-1-ol (1·0 c.c.) was treated with a solution of carrier-free [^{131}I]iodine in butan-1-ol (0·5 c.c.). A similar experiment with carbon tetrachloride as solvent was also set up, together with control tubes containing no quinone in each case. All tubes were shaken overnight under a tungsten lamp and then the solutions were extracted with aqueous sodium thiosulphate (4 times). There was no difference in the radioactivity associated with either phase between the controls and the experimental tubes.

Experiments in which a molar amount of carrier iodine was added gave similar negative results.

(*b*) The phosphate (8 mg.) in water (1 c.c.) was treated with carrier-free [^{131}I]iodine in carbon tetrachloride in the presence of buffers at pH 4, 6, and 9. The tubes were shaken overnight under a tungsten lamp and later examination revealed that no radioactivity was asociated with the aqueous phases. Similar results were obtained with butan-1-ol as the solvent or with the addition of carrier iodine.

Similar experiments with 2-methyl-1 : 4-naphthaquinone or the corresponding quinol bis-(disodium phosphate) were carried out in an attempt to introduce iodine directly into the molecule. All failed.

5 : 8-*Dihydro-2-methyl-1* : 4-*naphthaquinol.*—The following modification of the published procedure [20] proved effective. The Diels–Alder adduct of toluquinone and butadiene (16 g.) was dissolved in acetic acid (25 c.c.) and brought to incipient boiling. Hydrobromic acid in acetic acid (10 drops; 50% w/v) was added and a vigorous reaction took place. The quinol crystallized immediately and, when cool, was filtered off, washed with alcohol, and dried at 70° (yield 13·7 g., 86%); it had m. p. 172—173° and ultraviolet max. at 290 mμ (ε 3300) in 95% alcohol.

5 : 8-*Dihydro-2-methyl-1* : 4-*naphthaquinol Bis(dihydrogen Phosphate).*—The above quinol (6·0 g.) was phosphorylated by the method detailed above, the dibarium salt being isolated by addition of an equal volume of alcohol to its aqueous solution. After centrifuging, washing, and drying, the salt weighed 19·7 g. (96%). The dibarium salt in water was treated with dilute sulphuric acid until free from barium ions, the mixture filtered, and the filtrate evaporated to dryness *in vacuo* under nitrogen at about 50°. The residue was taken up in a little methyl alcohol, and *cyclo*hexylamine (3 c.c.) added. The *tetracyclohexylamine salt* of the bis(dihydrogen phosphate) crystallized in colourless prisms, which were washed with a little methyl alcohol. The yield (from 3 g. of the barium salt) was 1·8 g.(48%) and the m. p. *ca.* 212° (decomp.) dependent on the rate of heating. For analysis, the compound was dissolved in a little warm methyl alcohol, and excess of *cyclo*hexylamine added, the common ion effect assisting crystallization; m. p. was then 213° (decomp.) (Found, in material dried *in vacuo* at room temperature: C, 55·1; H, 9·05; N, 7·4; P, 7·95. $C_{11}H_{14}O_8P_2,4C_6H_{13}N,1\frac{1}{2}H_2O$ requires C, 55·3; H, 9·1; N, 7·4; P, 8·15%). Ultraviolet max. at 280 mμ (ε 1000) in 95% alcohol, at 272 mμ (ε 770) in 0·1N-HCl.

The *monocyclohexylamine salt* was prepared as follows: the tetra*cyclo*hexylamine salt (1·0 g.) was dissolved in water (3 c.c.), and 7N-sulphuric acid (3 c.c.) added. The product crystallized and was washed with a little water and then with alcohol (yield, 400 mg., 69%), forming prisms, m. p. 211—212° (Found, in material dried *in vacuo* at room temperature: C, 45·9; H, 6·5; N, 3·4; P, 13·4%; equiv., 153. $C_{11}H_{14}O_8P_2,C_6H_{13}N,\frac{1}{2}H_2O$ requires C, 46·0; H, 6·3; N, 3·2; P, 13·9%; equiv., 153).

3 : 6 : 7-*Tribromo-5* : 6 : 7 : 8-*tetrahydro-2-methyl-1* : 4-*naphthaquinol.*—5 : 8-Dihydro-2-methyl-1 : 4-naphthaquinol (1·0 g.) was suspended in ether (8 c.c.) and shaken with bromine (0·91 g.) in acetic acid (3 c.c.) until dissolved. An equal amount of bromine in acetic acid was then added, whereupon crystallization immediately ensued. The tan prisms were filtered off and washed with alcohol giving 2·0 g. (85%) of material which decomposed when heated but had no m. p. up to 300°. Before analysis, the *compound* was recrystallized twice from *tert.*-amyl alcohol (Found, in material dried *in vacuo* at room temperature: C, 32·1; H, 2·9; Br, 58·4. $C_{11}H_{11}O_2Br_3$ requires C, 31·8; H, 2·7; Br, 57·8%). Ultraviolet max. at 290 mμ (ε 4600) in 95% alcohol.

3-*Bromo-5* : 8-*dihydro-2-methyl-1* : 4-*naphthaquinone.*—The above tribromoquinol (1·0 g.) and sodium iodide (2·0 g.) were refluxed overnight in acetone (8 c.c.), then poured into aqueous sodium thiosulphate, and the whole was extracted twice with ether. The washed extract was oxidized by shaking it with acidified potassium dichromate solution after which the yellow ether layer was separated, washed free from acid with water, dried, and evaporated.

The yellow residue recrystallized from alcohol, from which the *compound* separated in needles, originally yellow, but becoming black when kept. The yield was 500 mg. (82%) and the m. p. 142° (decomp.) after sintering at 137°. The m. p. was unchanged by further recrystallizations (Found, in material dried *in vacuo* at room temperature: C, 52·45; H, 3·8; Br, 31·8. $C_{11}H_9O_4Br$ requires C, 52·1; H, 3·6; Br, 31·6%). Ultraviolet max. at 267 mμ (ε 10,500). When kept, the compound darkens considerably, the m. p. changes, and the absorption begins to resemble that of 3-bromo-2-methyl-1 : 4-naphthaquinone (see below). The maxima of black needles three weeks after preparation were at 245 (ε 7300) and 280 mμ (ε 8000) in 95% alcohol.

Oxidation of the above compound by chromic acid in acetic acid at 90° gave, after dilution with water, filtration, and recrystallization of the yellow solid from alcohol, 3-bromo-2-methyl-1 : 4-naphthaquinone, m. p. 154·5° undepressed on admixture with an authentic specimen. The ultraviolet absorption maxima of this quinone are at 245 (ε 13,800) and 280 mμ (ε 13,200) in 95% alcohol.

2 : 3 : 6 : 7-*Tetrabromo*-2 : 3 : 5 : 6 : 7 : 8-*hexahydro*-2-*methyl*-1 : 4-*naphthaquinone*.—5 : 8-Dihydro-2-methyl-1 : 4-naphthaquinol (1·0 g.) was dissolved in hot acetic acid (10 c.c.) and water (10 c.c.), and treated with bromine (2·8 g.) in acetic acid (1 c.c.). The mixture was boiled for a few seconds and allowed to cool. The *compound* crystallized on cooling as very pale yellow plates (1·7 g., 61%), m. p. 138—139° (decomp.) after sintering at 135°. After two recrystallizations from alcohol, the compound formed colourless plates, m. p. 148—149° (decomp.), after sintering at 135° (Found, in material dried *in vacuo* at 50°: C, 26·7; H, 2·2; Br, 64·3. $C_{11}H_{10}O_2Br_4$ requires C, 26·75; H, 2·0; Br, 64·8%). Ultraviolet max. at 275 mμ (ε 5300) in 95% alcohol. The compound was insoluble in aqueous alkali and was recovered unchanged after being shaken in ether with acidified potassium dichromate solution. Hot acetic acid containing anhydrous sodium acetate appeared to decompose the compound.

6 : 7-*Dibromo*-5 : 6 : 7 : 8-*tetrahydro*-2-*methyl*-1 : 4-*naphthaquinone*.—The above tetrabromo-compound (1·0 g.) and sodium iodide (2·0 g.) were mixed with acetone (20 c.c.). Free iodine was liberated at once. The whole was gently refluxed for 30 min., poured into aqueous sodium thiosulphate, and extracted with ether. The washed, dried, and evaporated extract gave a crystalline residue which recrystallized from alcohol, giving the *compound* (350 mg., 52%) as deep yellow rods, m. p. 72—73° unchanged by further recrystallization from alcohol (Found, in material dried *in vacuo* at room temperature: C, 40·2; H, 3·35; Br, 47·8. $C_{11}H_{10}O_2Br_2$ requires C, 39·5; H, 3·0; Br, 47·8%). Ultraviolet max. at 255 mμ (ε 24,000) in 95% alcohol. The compound decomposed when kept to a material only partly soluble in alcohol and of indefinite m. p. (84° upwards).

When the tetrabromo-compound (3·0 g.) and sodium iodide (9·0 g.) were refluxed for 24 hr. in acetone (140 c.c.), and the resulting mixture was poured into water, a yellow solid separated which darkened rapidly in air. This solid was dissolved in acetic acid (10 c.c.) and treated with a solution of chromic acid in acetic acid, the temperature being kept at 50°. Next morning the dark solution was poured into water, and the yellow crystals which separated were filtered off, washed with water, and dried (yield, 400 mg., 38%; m. p. 105—106°). Recrystallized from alcohol it had m. p. 107—109° alone or mixed with 2-methyl-1 : 4-naphthaquinone.

3 : 6 : 7-*Tribromo*-5 : 6 : 7 : 8-*tetrahydro*-2-*methyl*-1 : 4-*naphthaquinone*.—3 : 6 : 7-Tribromo-5 : 6 : 7 : 8-tetrahydro-2-methyl-1 : 4-naphthaquinol (3·5 g.) was shaken with ether (200 c.c.) and a solution of potassium dichromate (5 g.) and sulphuric acid (2 c.c.) in water (50 c.c.) till no further colour change took place. The yellow ether layer was washed free from acid with water, dried, and evaporated. The yellow residue was recrystallized from toluene–alcohol, giving the *compound* as yellow prisms (2·7 g., 78%), m. p. 141—142° (Found, in material dried *in vacuo* at room temperature: C, 32·3; H, 2·4; Br, 57·2. $C_{11}H_9O_2Br_3$ requires C, 32·0; H, 2·2; Br, 58·1%). Ultraviolet max. at 275 mμ (ε 12,900) in 95% alcohol. The same compound was prepared by the action of hot bromine in acetic acid on the quinol.

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362. *Complex Fluorides. Part VI.* The Properties of Silver Salts of Fluoro-acids and their Interaction with Aromatic Hydrocarbons.*

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Earlier work on the interaction of silver salts and aromatic hydrocarbons is reviewed briefly. Silver fluoroborate and hexafluoro-phosphate, -arsenate, -antimonate, -niobate, and -tantalate are soluble in benzene, toluene, and *m*-xylene, and many complexes have been prepared. Infrared absorption spectra and partial structure determinations have shown that the silver salts have ionic structures. The silver ion–aromatic hydrocarbon interaction energy is discussed, and it is suggested that the bonds formed must be of the same order of strength as ordinary covalent bonds.

The remarkable solubility of silver perchlorate in benzene was first studied by Hill,[1,2] who showed that such substances form a complex, $AgClO_4,C_6H_6$. Silver perchlorate and toluene form an analogous compound.[3] Silver perchlorate is soluble in *m*-xylene,[4] silver trifluoroacetate [5] and trichloroacetate [6] in benzene, and silver fluoroborate monohydrate is readily soluble in benzene [7] and toluene; [8] with the preparation of anhydrous silver fluoroborate (from silver borate and bromine trifluoride) and the demonstration that it is soluble in benzene, toluene, and ether,[9] the similarity between this substance and silver perchlorate is well established. The only other silver salts known to be soluble in aromatic hydrocarbons are the trifluoromethanesulphonate (in benzene) [10] and heptafluorobutyrate.[11] Complexes of the trifluoroacetate and the heptafluorobutyrate with benzene, toluene, the xylenes, and mesitylene have been characterised.[11]

Although freezing points,[1] dielectric properties,[12] and conductivities [13] of solutions of silver perchlorate in benzene indicate that, at low concentrations, the substance is present as ion-pairs, the possibility of covalent-bond formation, especially at high concentrations, between an oxygen atom of the perchlorate ion and the silver ion cannot be eliminated. Similar considerations apply to salts of carboxylic and sulphonic acids. The study of silver salts of complex fluoro-acids, however, is unlikely to be open to the same complication: covalent-bond formation in them would involve either bivalent fluorine, or gross distortion (detectable by *X*-ray or spectroscopic methods) of the complex ion and bond formation between silver and the central atom of the anion. The instance of the fluoroborate is particularly convincing: the hypothetical compound HBF_4 cannot be formulated without the use of bivalent fluorine or quinquevalent boron, and the failure of hydrogen fluoride and boron trifluoride to combine in equimolecular proportions is thus easily understandable.[14] Compounds are formed between these substances only if a donor molecule (*e.g.*, hydrogen fluoride, water, or ammonia) is available to co-ordinate with the proton. This paper describes the results of a survey of the structures and infrared spectra of silver salts of complex fluoro-acids, and their interaction with aromatic hydrocarbons. Further physicochemical studies will be described later.

Silver fluoroborate and hexafluoro-phosphate, -arsenate, -antimonate, -niobate, and -tantalate are all soluble in benzene, toluene, and *m*-xylene, the solubilities being

* Part V, *J.*, 1956, 1242.

[1] Hill, *J. Amer. Chem. Soc.*, 1921, **43**, 254.
[2] *Idem*, *ibid.*, 1922, **44**, 1163.
[3] Hill and Miller, *ibid.*, 1925, **47**, 2702.
[4] Spurgeon, Thesis, University of Michigan, 1941.
[5] Swarts, *Bull. Soc. chim. Belg.*, 1939, **48**, 176.
[6] Davidson and Sutton, *J.*, 1942, 565.
[7] Haunschild, Thesis, University of Cincinnati, 1948.
[8] Warf, *J. Amer. Chem. Soc.*, 1952, **74**, 3702.
[9] Sharpe, *J.*, 1952, 4538.
[10] Haszeldine and Kidd, *J.*, 1954, 4228.
[11] Tildesley and Sharpe, *Research*, 1954, **7**, S9.
[12] Hooper and Kraus, *J. Amer. Chem. Soc.*, 1934, **56**, 2265.
[13] Luder, Kraus, Kraus, and Fuoss, *ibid.*, 1936, **58**, 255.
[14] Sharpe, "Fluorine Chemistry," ed. Simons, Academic Press, New York, 1954, Vol. II.

greatest in toluene and least in benzene. The hexafluorophosphate, like silver trifluoroacetate, is also soluble in mesitylene. (For a discussion of the effect of steric hindrance by methyl groups on silver ion–aromatic hydrocarbon interaction see ref. 11.) The complexes obtained when these solutions are evaporated in a stream of dry nitrogen at room temperature are:

B =	benzene		toluene		*m*-xylene		mesitylene
	$2AgBF_4,3B$	$AgAsF_6,2B$	$2AgBF_4,3B$	$AgAsF_6,2B$	$AgBF_4,2B$	$AgAsF_6,2B$	$AgPF_6,3B$
	$AgPF_6,2B$	$AgSbF_6,2B$	$AgPF_6,2B$	$AgSbF_6,2B$	$AgPF_6,2B$	$AgSbF_6,2B$	
	$AgNbF_6,2B$						
	$AgTaF_6,2B$						

Silver hexafluorovanadate and tetrafluoroaurate react with the solvents and no complexes can be isolated.

Silver fluoroborate crystallises at room temperature in the orthorhombic system, with $a = 7{\cdot}75$, $b = 5{\cdot}54$, $c = 7{\cdot}16$ Å, and is isomorphous with potassium, rubidium, and ammonium fluoroborate. Silver hexafluorophosphate is isomorphous [15] with α-potassium hexafluorophosphate,[16] silver hexafluoroarsenate with a group of sodium salts of general formula $NaXF_6$,[15] and silver hexafluoroantimonate with the corresponding potassium salt.[17,18] Finally, silver hexafluoroniobate and hexafluorotantalate (which have the cæsium chloride structure, with $a = 9{\cdot}93$ Å for both compounds) are isomorphous with the analogous potassium salts.[18]

Coté and Thompson found that below 1400 cm.$^{-1}$ the infrared spectra of ammonium, potassium, and rubidium fluoroborate are identical;[21] in this region the spectrum of the silver salt is the same as those of the other three salts. Furthermore, silver hexafluorophosphate and hexafluoroarsenate have infrared spectra almost identical with those of the corresponding rubidium and cæsium compounds. The formulation of these silver salts as having purely ionic anion–cation bonding is thus further substantiated by their infrared spectra.

The interaction between the silver ion and unsaturated or aromatic hydrocarbons has been considerably discussed, the latest account being by Mulliken,[22] who derived theoretically the stereochemical configuration found in the silver perchlorate–benzene complex by Rundle and Goring.[23] In this compound, each silver ion is so bonded to two benzene molecules that the angle made by the silver ion with the middle of the nearest carbon–carbon bond and the centre of the aromatic ring is 100°; the shortest Ag–C distance is *ca.* 2·6 Å. Despite the magnitude of this distance, the silver ion–aromatic nucleus interaction energy should be fairly high in order to compensate for the work done in "diluting" the electrostatic lattice with uncharged molecules.[11] This argument is valid, however, only if no covalent bond is formed between silver and anion; this cannot be established for silver perchlorate, but in the fluoroborate the reasons advanced above make any such bond formation extremely improbable. Complex formation between silver salts of fluoroacids and aromatic hydrocarbons therefore indicates the need for a moderate bond energy between the silver ion and the hydrocarbon molecule.

A similar conclusion has been reached in a discussion of the closely related interaction of silver ion in aqueous solution and olefins.[24] From the temperature dependence of the distribution of trimethylethylene and *cyclo*hexene between carbon tetrachloride and aqueous silver nitrate, Winstein and Lucas [25] found the heat of the reaction $Ag^+(aq) + B = AgB^+(aq)$ (where B represents the olefin) to be about 6 kcal. As these authors pointed out, however,

[15] Cox, *J.*, 1956, 876.
[16] Bode and Clausen, *Z. anorg. Chem.*, 1951, **265**, 229.
[17] Bode, *ibid.*, 1951, **267**, 62.
[18] Bode and Voss, *ibid.*, 1951, **264**, 144.
[19] Brackken and Harang, *Z. Krist.*, 1930, **75**, 538.
[20] Hermann and Ilge, *ibid.*, 1931, **75**, 41.
[21] Coté and Thompson, *Proc. Roy. Soc.*, 1951, *A*, **210**, 217.
[22] Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811.
[23] Rundle and Goring, *ibid.*, 1950, **72**, 5337.
[24] Tildesley and Sharpe, *Research*, 1953, **6**, S51.
[25] Winstein and Lucas, *J. Amer. Chem. Soc.*, 1938, **60**, 836.

this value takes no account of the energy required for the partial displacement of water from the ion's neighbourhood. The silver–olefin bond energy should thus be much greater than 6 kcal.

Experimental

Preparations involving the use of bromine trifluoride and *X*-ray powder photographic investigations were carried out as described previously.[23] All operations on the silver salts, which are very deliquescent, and on their complexes with aromatic hydrocarbons, which are decomposed by moisture, were conducted with "dry-box" techniques. Infrared spectra were measured on Nujol or hexachlorobutadiene mulls, a Perkin-Elmer Model 21 Spectrometer with rock-salt optics being used. Complexes were prepared by dissolving silver salts in hot hydrocarbons, cooling the solutions in a stream of dry nitrogen, and removing the solvent on a porous tile. Reproducible results were thus obtained.

Preparations.—Silver fluoroborate was made as described previously [9] (Found: Ag, 54·8. Calc. for $AgBF_4$: Ag, 55·3%). Complexes were analysed by boiling them with water to remove as much of the hydrocarbon as possible, followed by gravimetric determination of silver (Found, for the *benzene complex*: Ag, 34·7. $2AgBF_4,3C_6H_6$ requires Ag, 34·5%. Found, for the *toluene complex*: Ag, 33·3. $2AgBF_4,3C_7H_8$ requires Ag, 32·5%. Found, for the m-*xylene complex*: Ag, 25·5. $AgBF_4,2C_8H_{10}$ requires Ag, 26·5%).

Silver hexafluorophosphate was obtained from silver powder, phosphoric oxide, and bromine trifluoride; this modification of Emeléus and Woolf's procedure [26] gave an almost white product (Found: Ag, 41·5. Calc. for $AgPF_6$: Ag, 42·7%) (Found, for the *benzene complex*: Ag, 26·6. $AgPF_6,2C_6H_6$ requires Ag, 26·4%. Found, for the *toluene complex*: Ag, 25·4. $AgPF_6,2C_7H_8$ requires Ag, 24·7%. Found, for the m-*xylene complex*: Ag, 23·3. $AgPF_6,2C_8H_{10}$ requires Ag, 23·2%. Found, for the *mesitylene complex*: Ag, 18·6. $AgPF_6,3C_9H_{12}$ requires Ag, 17·6%).

Silver hexafluoroarsenate was obtained from silver, arsenious oxide, and bromine trifluoride [26] (Found: Ag, 35·9. Calc. for $AgAsF_6$: Ag, 36·4%) (Found, for the *benzene complex*: Ag, 23·0. $AgAsF_6,2C_6H_6$ requires Ag, 23·8%. Found, for the *toluene complex*: Ag, 21·4. $AgAsF_6,2C_7H_8$ requires Ag, 22·4%. Found, for the m-*xylene complex*: Ag, 20·5. $AgAsF_6,2C_8H_{10}$ requires Ag, 21·2%).

The hexafluoroantimonate was prepared according to Woolf and Emeléus's [24] directions (Found: Ag, 31·7. Calc. for $AgSbF_6$: Ag, 31·4%) (Found, for the *benzene complex*: Ag, 20·9. $AgSbF_6,2C_6H_6$ requires Ag, 21·6%. Found, for the *toluene complex*: Ag, 19·9. $AgSbF_6,2C_7H_8$ requires Ag, 20·4%. Found, for the m-*xylene complex*: Ag, 19·3. $AgSbF_6,2C_8H_{10}$ requires Ag, 19·4%).

Silver hexafluoro-niobate and -tantalate were prepared by Gutmann and Emeléus's method [27] (Found: Nb, 30·2. Calc. for $AgNbF_6$: Nb, 29·6%. Found: Ta, 45·3. Calc. for $AgTaF_6$: Ta, 45·0%). These substances were soluble in benzene, toluene, and *m*-xylene, but on warming them with toluene and *m*-xylene decomposition occurred and no complexes were isolated (Found, for the *benzene complex*: Nb, 20·2. $AgNbF_6,2C_6H_6$ requires Nb, 19·8%. Found, for the *benzene complex*: Ta, 31·7. $AgTaF_6,2C_6H_6$ requires Ta, 32·4%).

Silver hexafluorovanadate [28] and tetrafluoroaurate [29] were made by methods described previously; both reacted with aromatic hydrocarbons, and no complexes were isolated.

X-*Ray Powder Photography.*—Unit-cell dimensions have been given on p. 1856. The interpretation of the powder pattern of silver fluoroborate was made possible by its similarity to those of potassium and ammonium fluoroborates, the structures of which were known.[30, 31]

Infrared Absorption Spectra.—Silver fluoroborate shows absorption maxima at **769, 1026, 1064, 1300, 1529,** and **3509** cm.$^{-1}$. Since no data were available for hexafluorophosphates, the rubidium and cæsium salts were prepared from alkali-metal halides, phosphoric oxide, and bromine trifluoride; PF_6^- was determined as the nitron salt (Found: PF_6^-, 63·0. Calc. for $RbPF_6$: PF_6^-, 62·9%. Found: PF_6^-, 50·6. Calc. for $CsPF_6$: PF_6^-, 52·1%). Spectra recorded were: $AgPF_6$, broad peak at 830—840 cm.$^{-1}$, subsidiary peak at 740 cm.$^{-1}$; $RbPF_6$, broad peaks at 845, 802 cm.$^{-1}$, subsidiary peak at 740—720 cm.$^{-1}$; $CsPF_6$, broad peaks at 843, 802 cm.$^{-1}$, subsidiary peak at 740—720 cm.$^{-1}$.

[26] Woolf and Emeléus, *J.*, 1949, 2865; 1950, 1050.
[27] Gutmann and Emeléus, *J.*, 1950, 1046.
[28] Emeléus and Gutmann, *J.*, 1949, 2979.
[29] Sharpe, *J.*, 1949, 2901.
[30] Hoard and Blair, *J. Amer. Chem. Soc.*, 1935, **57**, 1985.
[31] Pesce, *Gazzetta*, 1930, **60**, 936.
[23] Sharpe, *J.*, 1950, 3444; Cox and Sharpe, *J.*, 1954, 1798.

Analogous preparations were made, for the same reason, in the hexafluoroarsenate series (Found: As, 26·9. Calc. for $RbAsF_6$: As, 27·3%. Found: As, 23·1. Calc. for $CsAsF_6$: As, 23·3%). Spectra recorded were: $AgAsF_6$, broad peak at 695 cm.$^{-1}$; $RbAsF_6$, broad peak at 700 cm.$^{-1}$, subsidiary peaks at 1295, 1064, 972, and 827 cm.$^{-1}$; $CsAsF_6$, broad peak at 699 cm.$^{-1}$, subsidiary peaks at 1300, 1068, 970, and 823 cm.$^{-1}$.

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363. *Complex Fluorides. Part VII.* The Interaction of Cuprous Salts of Fluoro-acids and Aromatic Hydrocarbons.*

By D. W. A. Sharp and A. G. Sharpe.

Copper displaces silver from solutions of silver fluoroborate, fluorosulphonate, and hexafluoro-phosphate, -arsenate, -niobate, and -tantalate in toluene, forming the corresponding cuprous compounds. The implications of these observations are discussed.

The formation of complexes between cuprous salts and olefins is well established. Cuprous chloride forms addition products with ethylene, propene, and *iso*butene under pressure, but the products are unstable at ordinary temperature and pressure.[1,2] Water-soluble complexes of cuprous ion and unsaturated alcohols or carboxylic acids have also been reported.[3–5] It is only recently, however, that a cuprous salt has been shown to form a complex with an aromatic hydrocarbon.

Warf [6] obtained a solution containing cuprous fluoroborate in toluene by decomposition of a solution of an aryldiazonium fluoroborate in boiling toluene in the presence of copper powder, and also by the action of boron trifluoride on a mixture of equivalent quantities of copper powder and cupric fluoride suspended in toluene. Recent investigations [8] of the interaction of silver salts of complex fluoro-acids and aromatic hydrocarbons suggested that solutions of the analogous cuprous complexes might be obtained by displacement of silver by copper, a method used to prepare a solution of cuprous nitrate in acetonitrile.[7]

This method was applied to the preparation of solutions of cuprous fluoroborate, fluorosulphonate, and hexafluoro-phosphate, -arsenate, -niobate, and -tantalate in toluene. The solutions are colourless, and the oxidation state of the copper in the fluoroborate has been established by the determination of the equivalent weight of the copper which goes into solution, and by the diamagnetism of the solution (all cupric compounds are paramagnetic). Dry solutions of all the cuprous compounds are stable indefinitely, but on addition of water disproportionation takes place, with the formation of metallic copper, toluene, and a hydrated cupric salt. Solid cuprous salts have not been obtained by evaporation of toluene solutions; when attempts were made to remove the solvent in a stream of dry nitrogen at room temperature or *in vacuo*, colourless solids were deposited, but these rapidly turned brown as disproportionation occurred. These observations are similar to Morgan's [7] on the impossibility of isolating cuprous nitrate from solution in acetonitrile.

* Part VI, preceding paper.

[1] Tropsch and Mattox, *J. Amer. Chem. Soc.*, 1935, **57**, 1102.
[2] Gilliland, Seebold, Fitz-Hugh, and Morgan, *ibid.*, 1939, **61**, 1960.
[3] Andrews and Keefer, *ibid.*, 1948, **70**, 3261; 1949, **71**, 2379.
[4] Keefer, Andrews, and Kepner, *ibid.*, 1949, **71**, 2381.
[5] Kepner and Andrews, *J. Org. Chem.*, 1948, **13**, 208.
[6] Warf, *J. Amer. Chem. Soc.*, 1952, **74**, 3702.
[7] Morgan, *J.*, 1923, 2901.
[8] Sharp and Sharpe, preceding paper.

It has been argued [8] that for a salt such as silver fluoroborate, covalent-bond formation between anion and cation is exceedingly unlikely, and a similar argument should apply to cuprous salts of complex fluoro-acids. The formation of a solvated silver or cuprous ion in toluene may be regarded as taking place in the following stages (M = Ag or Cu) :

$$M_{(s)} \longrightarrow M_{(g)} \longrightarrow M^{+}_{(g)} \longrightarrow M^{+}_{(solv.)}$$

The first stage involves the absorption of the latent heat of sublimation of the metal, the second stage the absorption of energy equivalent to the first ionisation potential. Both quantities for copper (81·5 and 260·8 kcal., respectively) exceed those [9] for silver (69·1 and 245·3 kcal.). Owing to experimental difficulties, the heat of the displacement reaction has not been measured, but if we make the reasonable assumption that the reaction is thermoneutral or exothermic, and that the structures (and hence the entropies) of the solvated cations are not very different, the heat of solvation of the cuprous ion should be greater than that of the silver ion by at least 20 kcal./g.-ion.

This argument suggests a method of obtaining information about the nature of the aromatic hydrocarbon–metal ion interaction. If the bonding electrons are provided exclusively by the hydrocarbon, complex formation by cuprous salts should result in a much larger decrease in the aromatic C–C vibration frequency than complex formation by silver salts. If, on the other hand, the *d*-electrons of the metal ion are used, such a decrease might, but would not necessarily, occur. This should be shown by comparison of the Raman spectra of concentrated solutions of cuprous and silver fluoroborates in toluene.

Experimental

Silver salts were prepared as described in Part VI.[8] Silver fluorosulphonate was obtained by Woolf's method [10] (Found : Ag, 52·2. Calc. for $AgSO_3F$: Ag, 52·1%); it was soluble in benzene, toluene, *m*-xylene, and mesitylene. The use of bromine trifluoride in the preparation ensured the dryness of the silver salts; toluene was dried over sodium; copper powder was dried at 130° and preserved over phosphoric oxide. All additions of reagents and filtrations were carried out in a " dry-box "; sintered-glass filters were used since filter papers contain sufficient moisture to effect partial disproportionation of cuprous compounds in toluene.

In a typical experiment, excess of copper powder, followed by toluene, was added to a known weight of silver fluoroborate in a glass tube. The whole was shaken for 2 days, after which no silver remained in the solution. The excess of copper was filtered off, and copper in the filtrate (found by the Gouy method to be diamagnetic) was determined iodometrically after oxidation to the cupric state [Found : equiv. of dissolved Cu (Ag = 108), 58·8. Calc. for Cu^+ : 63·5]. No solid cuprous salts were obtained.

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University Chemical Laboratory, Cambridge. [*Received, December 19th*, 1955.]

[9] Nat. Bur. Stand. Tables, Circular 500.
[10] Woolf, *J.*, 1950, 1053.

364. *The Chemistry of the Transition Elements. Part I. Dimeric Carbonyl Complexes of Platinum.*

By R. J. Irving and E. A. Magnusson.

Physical and chemical evidence for the assignment of the "*trans*-symmetrical" structure of the compounds $[Pt(CO)Cl_2]_2$, $[Pt(CO)Br_2]_2$, and $[Pt(CO)I_2]_2$ is presented.

The reaction of neutral ligands with these compounds leads to derivatives of the types : (i) $Pt(CO)Hal_2L$, where Hal = Cl, Br, or I, and L = a monodentate donor group; and (ii) $[Pt(CO)HalLL]^+[Pt(CO)Hal_3]^-$, where LL = a bidentate donor group.

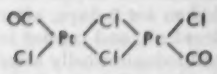
The reaction between platinum, carbon monoxide, and chlorine was discovered by Schutzenberger [1] who isolated the compounds $Pt(CO)Cl_2$, $Pt(CO)_2Cl_2$, and $Pt_2(CO)_2Cl_4$. This and later work on platinum carbonyl compounds has been summarized by Sidgwick.[2]

For some time past the compound whose empirical formula is $Pt(CO)Cl_2$ has been assumed to be dimeric, and Chatt and Williams [3] have pointed to the similarity of properties of this compound and certain "*trans*-symmetrical" platinum(II)–phosphorus trifluoride, –(tertiary phosphine), and –(tertiary arsine) complexes.

Of the three compounds, $Pt(CO)Cl_2$, $Pt(CO)Br_2$, and $Pt(CO)I_2$, the bromide is the only one suitable for molecular-weight determination and even this, owing to its instability and the fact that its saturated solution in benzene at 25° is only 0·035M, gives rather unreliable results. However, the value obtained (750 ± 50) shows that the molecule is definitely dimeric. The analogous physical and chemical properties of the compounds indicate that the chloride and iodide are also dimeric, the general formula being $[Pt(CO)Hal_2]_2$.

Metal carbonyls give rise to sharp absorption bands in the region 2000—2100 cm.$^{-1}$ of the infrared spectrum.[4] Absorption in this region has been shown to indicate terminal carbon monoxide ligands, while a bridging carbonyl group, as in iron enneacarbonyl, absorbs at about 1820 cm.$^{-1}$. Absence of the latter frequency (see Table) shows that, in the dimeric platinum carbonyl halides, the carbonyl groups must be terminal. The structure must therefore be halogen-bridged.

Dilute benzene solutions of each of the metal carbonyl halides exhibited no dielectric loss in the 10 cm. region, showing definitely that the compounds are non-polar and therefore have the annexed "*trans*-symmetrical" structure. A full discussion of the chemical evidence for halogen-bridged structures has been given by Chatt.[5]



Reaction of the bridged compound with two mols. of neutral monodentate ligand should give the derivative $Pt(CO)Hal_2L$ * and with one mol. of neutral bidentate ligand the salt $[Pt(CO)HalLL]^+[Pt(CO)Hal_3]^-$.*

Infrared absorption peaks (cm.$^{-1}$) in the carbonyl region.

(1)	$[Pt(CO)Cl_2]_2$	2152	
(2)	$[Pt(CO)Br_2]_2$	2130	
(3)	$[Pt(CO)I_2]_2$	2112	
(4)	$[Pt(CO)dipyCl]^+[Pt(CO)Cl_3]^-$	2145, 2102	
(5)	$[Pt(CO)dipyBr]^+[Pt(CO)Br_3]^-$	2132, 2096	
(6)	$[Pt(CO)dipyI]^+[Pt(CO)I_3]^-$	2115, 2072	
(7)	$PyH^+[Pt(CO)Cl_3]^-$	2106	
(8)	$PyH^+[Pt(CO)Br_3]^-$	2096	
(9)	$PyH^+[Pt(CO)I_3]^-$	2076	

In this way the compounds $Pt(CO)(MeAsPh_2)Hal_2$, $Pt(CO)tolI_2$ (tol = *p*-toluidine) and $[Pt(CO)dipyHal][Pt(CO)Hal_2]$ were prepared. The last compound is analogous to that which Chatt reported to be formed by the action of dipyridyl on $[Pt(PR_3)Cl_2]_2$. Addition

* Where L and LL indicate monodentate and bidentate ligands respectively.

[1] Schutzenberger, *Compt. rend.*, 1870, **70**, 1134, 1287; *Bull. Soc. chim. France*, 1870, **14**, 97.
[2] Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, London, 1950, Vol. I, pp. 1627—8.
[3] Chatt and Williams, *J.*, 1951, 3061.
[4] Brimm, Lynch, and Sesny, *J. Amer. Chem. Soc.*, 1954, **76**, 3831.
[5] Chatt, *J.*, 1951, 652.

to the bridged carbonyl of more than two mols. of ligand causes expulsion of carbon monoxide and formation of the compound PtL_2Hal_2.

This excess-ligand reaction does not take place with *p*-toluidine. Further, the *p*-toluidine compound is the most stable of all those prepared. This may be due to the weak *trans*-effect of *p*-toluidine; the CO group is thus not rendered labile and so replacement by *p*-toluidine is not possible.

It should be noted that all the carbonyl compounds are unstable to heat and moisture. The stability of the *p*-toluidine compound is therefore only relative.

The absorption maxima of 2102 and 2106 cm.$^{-1}$ for compounds 4 and 7 of the Table are obviously due to C–O stretching frequencies of carbon monoxide in the identical anions. Similarly, the frequencies 2096 and 2072 cm.$^{-1}$ can be assigned to carbon monoxide in the anions of compounds 5 and 6. Additional evidence for the assignment of the carbonyl frequencies in compounds 1, 2, and 3 to terminal carbonyl groups is that the absorptions are in the same region as those due to the carbonyl groups in compounds 4—9 where they are certainly terminal.

Experimental

Dicarbonyldichloro-μμ′-dichlorodiplatinum(II).—This compound was obtained by methods similar to those employed by Mylius and Foerster.[6] Dry chlorine and dry carbon monoxide were passed over finely divided platinum at about 250°. The yellow sublimate which was slowly formed was dissolved in concentrated hydrochloric acid, and the compound recovered by evaporation under reduced pressure. Alternatively the sublimate was heated at 200° in a stream of dry carbon dioxide, and the compound recrystallized from dry benzene. The yield is considerably better by the second method, but by using the first one may be sure that no dichlorodicarbonylplatinum(II) is present. The compound melts at 192° (Found: Cl, 24·2. Calc. for $C_2O_2Cl_4Pt_2$: Cl, 24·1%).

Dicarbonyldibromo-μμ′-dibromodiplatinum(II).—The yellow sublimate obtained by the action of carbon monoxide and chlorine on heated platinum was dissolved in the minimum quantity of hydrobromic acid and evaporated to dryness on the water-bath.[6] The bromide was recrystallized from dry benzene. The compound melts at 182° (Found: Pt, 50·6. Calc. for $C_2O_2Br_4Pt_2$: Pt, 50·9%).

Dicarbonyldi-iodo-μμ′-di-iododiplatinum(II).—This compound was prepared in the same way as the preceding one, with hydriodic acid in place of hydrobromic acid.[6] The iodide, recrystallized from dry benzene, decomposed between 135° and 140° (Found: I, 53·4; Pt, 40·6. Calc. for $C_2O_2I_4Pt_2$: I, 53·2; Pt, 40·9%).

Methyldiphenylarsinecarbonyldichloroplatinum(II).—Methyldiphenylarsine (0·72 g.) in carbon tetrachloride (50 ml.) was added to dicarbonyldichloro-μμ′-dichlorodiplatinum(II) (0·87 g.) in benzene (100 ml.). The initial yellow solution became paler. Crystals of methyldiphenylarsinecarbonyldichloroplatinum(II) were obtained with some difficulty from the residue. The compound gives a non-conducting solution in nitrobenzene (Found: C, 34·0; H, 2·6; Pt, 33·8. Calc. for $C_{14}H_{13}OAsCl_2Pt$: C, 31·2; H, 2·4; Pt, 36·25%). The analytical figures indicate contamination with about 0·1 mole of the tertiary arsine per mole of the platinum complex. It proved impossible to purify the compound further without some reduction to metallic platinum. The carbonyl frequencies in the infrared spectra of several preparations of the compound were identical.

Methyldiphenylarsinecarbonyldibromoplatinum(II).—Methyldiphenylarsine (0·64 g.) in carbon tetrachloride (100 ml.) was added to dicarbonyldibromo-μμ′-dibromodiplatinum(II) (1·00 g.) in a mixture of benzene (50 ml.) and carbon tetrachloride (100 ml.). The orange solution changed to yellow when warmed on the water-bath. Yellow needles of *methyldiphenylarsinecarbonyldibromoplatinum*(II) slowly crystallized. The compound is non-conducting in nitrobenzene (Found: C, 26·8; H, 2·1; Pt, 31·2. $C_{14}H_{13}OAsBr_2Pt$ requires C, 26·8; H, 2·1%; Pt, 31·1%).

Methyldiphenylarsinecarbonyldi-iodoplatinum(II).—Methyldiphenylarsine (0·26 g.) in benzene (50 ml.) was added to the dimeric iodide (0·54 g.) in benzene (100 ml.). On evaporation, the yellow solution became red and a red oil was obtained. This yielded brown crystals when kept in a dry sealed container in the refrigerator for several days. The *compound* gives a non-conducting solution in nitrobenzene (Found: C, 22·9; H, 1·4; Pt, 27·1. $C_{14}H_{13}OAsI_2Pt$ requires C, 23·3; H, 1·8; Pt, 27·1%).

[6] Mylius and Foerster, *Ber.*, 1891, **24**, 2424; Foerster, *ibid.*, p. 3751.

2 : 2′ - *Dipyridylcarbonylchloroplatinum*(II) *Carbonyltrichloroplatinate*(II).—2 : 2′ - Dipyridyl (0·11 g.) in benzene (50 ml.) was added to the dimeric chloride (0·43 g.) in benzene (200 ml.). A yellow precipitate was formed immediately. This was washed several times with dry benzene. The *compound* is itself sensitive to moisture, and is very often contaminated with decomposition products of the starting materials which are very difficult to remove. The conductivity of 31·4 mhos in M/1000-nitrobenzene solution shows the existence of two ions in solution (Found : Pt, 53·0. $C_{12}H_8O_2N_2Cl_4Pt_2$ requires Pt, 52·5%).

2 : 2′ - *Dipyridylcarbonylbromoplatinum*(II) *Carbonyltribromoplatinate*(II).—2 : 2′ - Dipyridyl (0·149 g.) in benzene (50 ml.) was added to the dimeric bromide (0·66 g.) in benzene (200 ml.). A yellow precipitate, formed immediately, was filtered off and washed with benzene. The *compound* is unstable to moisture. The conductivity of 31·6 r.o. in M/1000-nitrobenzene solution shows the existence of two ions in solution (Found : Pt, 42·0. $C_{12}H_8O_2N_2Br_4Pt_2$ requires Pt, 42·3%).

2 : 2′ - *Dipyridylcarbonyliodoplatinum*(II) *Carbonyltri-iodoplatinate*(II).—2 : 2′ - Dipyridyl (0·032 g.) in benzene (50 ml.) was added to the dimeric iodide (0·20 g.) in benzene (100 ml.). A yellow precipitate of the compound was formed. It is much more stable than the chloro- and bromo-compounds and can be recrystallized from boiling acetone. The conductivity of 24·2 mhos in M/1000-nitrobenzene solution shows the existence of two ions in solution (Found : C, 13·8; H, 0·8; N, 2·6; Pt, 34·6. Calc. for $C_{12}H_8O_2N_2I_4Pt_2$: C, 12·0; H, 0·7; N, 2·5; Pt, 34·4%).

Pyridinium carbonyltrichloroplatinate(II).—This compound was prepared according to the method of Mylius and Foerster[6] (Found : Pt, 46·8. Calc. for $C_6H_6ONCl_3Pt$: Pt, 47·8%). The conductivity in M/1000-nitrobenzene solution was 32·4 r.o.

Pyridinium carbonyltribromoplatinate(II).—Solid dicarbonyldibromo-μμ′-dibromodiplatinum(II) (0·3 g.) was added to a solution of pyridinium bromide (0·25 g.) in dilute hydrobromic acid. The solution was slowly evaporated to smaller bulk on the water-bath, filtered, and allowed to crystallize. Yellow needles of *pyridinium carbonyltribromoplatinate*(II) were obtained and were recrystallized from dilute hydrobromic acid. The conductivity in M/1000-nitrobenzene solution was 31·6 mhos (Found : Pt, 36·95. $C_6H_6ONBr_3Pt$ requires Pt, 36·9%).

Pyridinium carbonyltri-iodoplatinate(II).—This compound was prepared as above, with pyridinium iodide in place of the bromide. Orange needles were formed on recrystallization from dilute hydriodic acid. The compound decomposes, on storage, to pyridinecarbonyldi-iodoplatinum(II). The conductivity in M/1000-nitrobenzene solution was 31·0 mhos (Found : Pt, 27·5. Calc. for $C_6H_6ONI_3Pt$: Pt, 29·15%).

p-*Toluidinecarbonyldi-iodoplatinum*(II).—*p*-Toluidine (0·226 g.) in benzene (50 ml.) was added to dicarbonyldi-iodo-μμ′-di-iodoplatinum(II) (1·00 g.) in benzene (40 ml.). The solution changed colour from red to yellow and, after evaporation, masses of yellow fibres gradually separated. The *compound* was diamagnetic and a non-conductor in nitrobenzene. It was stable in air for a long period and was only slowly decomposed by water (Found : Pt, 33·2; I, 43·55. $C_9H_9ONI_2Pt$ requires Pt, 33·4; I, 43·45%).

Molecular Weights.—Many attempts were made to obtain molecular weights by the usual methods applied to inorganic compounds, notably cryoscopic and ebullioscopic methods. Not even very approximate results were possible owing to the instability of the compound sat higher temperatures and the insolubility at low temperatures. The Rast method with camphene (m. p. 48°) seemed to be applicable, but, at the low concentration obtained, results were meaningless. A result was finally obtained by the " isothermic microdistillation " method of Niederl and his co-workers.[7] In this method the capillary tubes, sealed at one end, are placed horizontally, sealed in a larger tube, with the solution of known molar concentration opposing that of the unknown compound. Three tubes were prepared, the same compound being used in each case, 0·015M (on a molecular weight of 766·14 for the bromide). The reference compound (benzoic acid) was prepared in three tubes with concentrations, 0·01M, 0·015M, and 0·02M. Although it is possible to obtain a solution of the bromide of 0·035M concentration, it was necessary to use this weaker solution because of the tendency of the solution to decompose at the liquid–gas interfaces. The lengths of the solution in the tubes were then measured at intervals. They varied as follows :

Strength of known soln.	Original	Final
0·010M	33·1 mm.	30·05 mm.
0·015M	25·0 mm.	25·0 mm.
0·020M	33·5 mm.	35·0 mm.

It was estimated that this indicated a molecular weight for the compound of 750 ± 50.

[7] Niederl, Kasanof, Kisch, and Subba Rao, *Mikrochemie*, 1949, **34**, 132.

Infrared Spectra.—Spectra were measured on a double-beam single-pass instrument designed and built in this School. Compounds were placed between rock-salt plates in paraffin mulls. A sodium chloride prism was used, and the instrument was calibrated with a Polystyrene film.

Dielectric-loss Measurements.—The measurements were made on saturated benzene solutions of the three compounds by a method analogous to that described by Willis Jackson [8] in an apparatus made available by the University of Sydney. The Debye equation for dilute solutions of polar molecules is : [9]

$$\frac{\Delta \tan \delta}{c} = \text{Molar loss tangent} = \frac{\varepsilon_0 + 2}{\varepsilon_0} \cdot \frac{\Pi N_0 \mu^2}{6750\, kT} \cdot \frac{\omega\tau}{1 + \omega^2\tau^2}$$

It is apparent, from this equation, that the molar loss will be zero when μ, the dipole moment, is zero. The measurements on the three compounds $[Pt(CO)Hal_2]_2$ thus clearly indicate the molecules to be non-polar.

The authors thank Professor R. J. W. Le Fèvre and Mr. Tardif for the dielectric-loss measurements, Mr. B. M. K. Gatehouse for some of the infrared measurements, and Dr. E. Challen for the C, H, and N microanalyses.

School of Applied Chemistry,
N.S.W. University of Technology, Sydney. [*Received, June 27th*, 1955.]

[8] Willis Jackson, *Discuss. Faraday Soc.*, 1946, **42**, A, 91, and other papers in the same volume.
[9] Davies, *Quart. Rev.*, 1954, **8**, 253.

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365. *The Morphine–Thebaine Group of Alkaloids. Part VI.* The Condensation of Thebaine with Dienophils.*

By K. W. Bentley and A. F. Thomas.

In a search for new analgesics the thebaine–*p*-benzoquinone adduct has been reduced to a dihydro-derivative, which is as active an analgesic in rats as pethidine. The thebaine–maleic anhydride adduct has been converted into the ester, and the latter reduced with lithium aluminium hydride to the corresponding diol. Condensation of thebaine with 1 : 2- and 1 : 4-naphthaquinone has been studied. Attempts to prepare adducts of β-ethylthiocodide failed.

Thebaine (I), pharmaceutically valueless, can be converted by condensation with dienophils into substances having the basic structure of codeine methyl ether, *e.g.*, thebaine–*p*-benzoquinone (II) and the thebaine–maleic anhydride adduct (III) (Sandermann;[1] Schöpf, von Gottberg, and Petri [2]). These compounds and their derivatives have now been tested for analgesic properties and their behaviour towards hot acids has been studied in relation to the transformation of the thebaine–quinol adduct (IV) into flavothebaone.[2]

Catalytic reduction of the *p*-benzoquinone adduct (II) afforded the 5′ : 6′-dihydro-derivative (V) whose structure was proved by failure of the product to undergo isomerisation by acid to a quinol derivative analogous to the quinol adduct (IV) and by the infrared spectrum (p. 1865). Attempts to reduce the ethylenic bridge of the dihydro-compound (V) failed and examination of a model showed that this bridge is so screened by the other parts of the molecule that adsorption on a catalyst would be very difficult. Demethylation of the dihydro-compound (V) by concentrated hydriodic acid or pyridine hydrochloride has so far not yielded pure material.

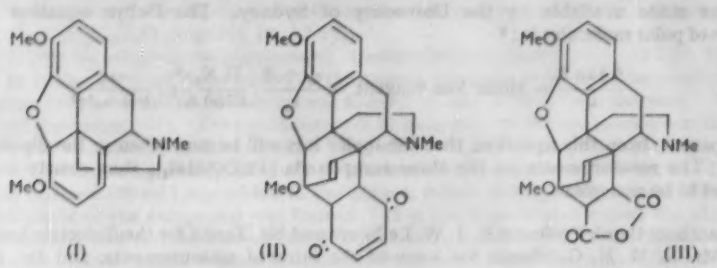
Only the keto-alcohol (VI) was obtained by reduction of the diketone (V) with sodium

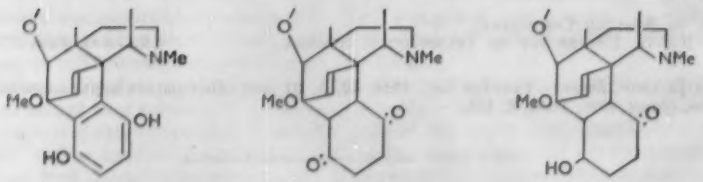
* Part V, *J.*, 1955, 3252.

[1] Sandermann, *Ber.*, 1938, **71**, 648.
[2] Schöpf, von Gottberg, and Petri, *Annalen*, 1938, **536**, 216.

borohydride; even when an excess was used, reduction of the least hindered of the two carbonyl groups is assumed.

In agreement with the findings of Schöpf, von Gottberg, and Petri [2] we have been unable to hydrogenate either the maleic anhydride adduct (III) or the diethyl maleate adduct (VII;

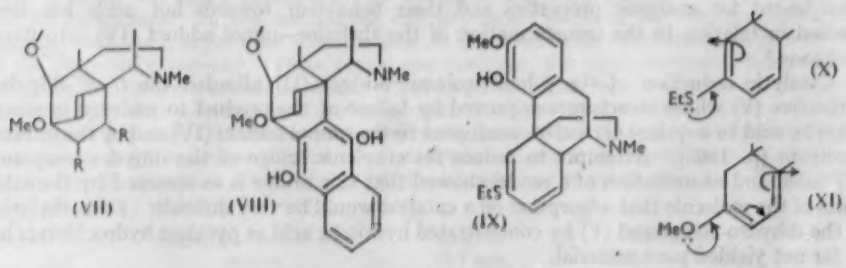




$R = CO_2Et$); the latter was, however, reduced by lithium aluminium hydride to the but-2-ene-1 : 4-diol "adduct" (VII, $R = CH_2{\cdot}OH$) (we are aware that this compound would very probably not be formed by the direct addition of but-2-ene-1 : 4-diol to thebaine, but the name used seems the most suitable in absence of fully systematic nomenclature). No rearrangement occurred when the maleic anhydride adduct was heated with concentrated hydrochloric acid or phosphoric acid, the product being the acid, which was identified by conversion into the ester (VII; $R = CO_2Et$).

A diastereoisomer of the ester (VII; $R = CO_2Et$), the fumarate adduct, was prepared by condensing thebaine with fumaryl chloride and esterifying the product, but the yields of ester obtained in different experiments varied enormously and the investigation was not pursued.

Condensation of thebaine with 1 : 4-naphthaquinone was reported by Sandermann [1] to give a colourless substance; this condensation could not be repeated according to Sandermann's directions, but treatment of the reaction mixture with acetic acid resulted in the



subsequent isolation of what is very probably the quinol isomer (VIII) of the initial condensation product. As in the thebaine–*p*-benzoquinone series [3] no methiodide could be prepared from the thebaine–1 : 4-naphthaquinone adduct, but 1 : 4-naphthaquinone and

[3] Bentley, Robinson, and Wain, *J.*, 1952, 958.

thebaine methiodide afforded a methiodide (orange, therefore presumably of the diketone form) which decomposed on recrystallisation, with regeneration of thebaine methiodide. Attempts under a variety of conditions to effect addition of thebaine to the less reactive 1 : 2-naphthaquinone failed.

It was therefore thought possible that β-ethylthiocodide (IX), which also contains a cyclic diene system, might give an adduct with *p*-benzoquinone, but attempts to bring this about failed, probably because only one double bond is activated by the EtS group in β-ethylthiocodide (X) and not the whole diene system as in thebaine (XI).

Pharmacological Testing.—The thebaine–*p*-benzoquinone adduct (II), like thebaine itself, caused convulsions in mice and rabbits, delayed in onset and usually commencing no sooner than ten minutes after intravenous injection. In mice the intravenous LD_{50} was approximately 20 mg./kg. The adduct also exhibited antihistamine properties, concentrations of 10^{-6} g./ml. almost eliminating the effect of histamine (5×10^{-7} g./ml.) on guinea-pig ileum and 3×10^{-7} g./ml. greatly reducing the response.

Pharmacological examination of thebaine–quinol adduct was limited by the low solubility of the base and its salts. Given as a suspension, 200 mg./kg. intraperitoneally produced no overt symptoms in mice. At a concentration of 10^{-5} g./ml. it decreased the motility of isolated ileum and greatly reduced the spasm caused by acetylcholine, histamine, or barium.

The 5′ : 6′-dihydro-compound (V) is a powerful analgesic, its potency being a tenth to a fifth of that of morphine by subcutaneous injection in rats (of the same order as that of pethidine). Its LD_{50} of 150 mg./kg. intravenously in mice is notably different from that of the unreduced compound (II). It showed no significant spasmolytic or antihistamine properties.

The thebaine–but-2-ene-1 : 4-diol " adduct " showed some analgesic effects in rats on subcutaneous injection of 25 mg./kg. The intravenous LD_{50} was about 70 mg./kg., hyperexcitability and Straub tail being observed. In a rabbit it was mildly depressant on intravenous injection, and was slightly mydriatic at 25 mg./kg. intraperitoneally in mice. At a concentration of 10^{-5} g./ml. it reduced the response of guinea-pig ileum to histamine and barium, but not to acetylcholine.

Experimental

Thebaine–p-Benzoquinone (III) (Sandermann;[1] Schöpf, von Gottberg, and Petri[3]).—It was more convenient to carry out this preparation in toluene in open vessels on the water-bath, than under reflux in benzene as previously reported. The product (98%) was obtained as lemon-yellow prisms, m. p. 268° (lit.,[3] 250°).

5′ : 6′-Dihydro-adduct of Thebaine and p-Benzoquinone (V).—The thebaine–*p*-benzoquinone adduct (6 g.) in cold glacial acetic acid (35 ml.) containing platinum oxide (0·1 g.) was shaken under hydrogen at atmospheric pressure until 1 mol. of hydrogen had been absorbed (325 ml. at N.T.P.). The mixture was filtered and diluted with water. On addition of ammonia white crystals were obtained. These were collected, washed with water, and recrystallised three times from 2-ethoxyethanol, the *5′ : 6′-dihydro-adduct* being obtained as colourless elongated plates, m. p. 222° (decomp.), $[\alpha]_D^{20}$ −246° (*c* 1·5 in $CHCl_3$) (Found: C, 71·5, 71·3; H, 6·4, 6·5; N, 3·1, 3·5. $C_{25}H_{27}O_5N$ requires C, 71·2; H, 6·5; N, 3·3%). The m. p. of this compound varied between 204° and 222° in different preparations, and also varied with the rate of heating. Preparations of differing m. p. did not depress each other's m. p., and their identity was confirmed by their infrared absorption spectra. These showed carbonyl absorption at 5·88 and 5·93 μ, proving the saturated ketone structure (IV) [the thebaine–*p*-benzoquinone adduct (II) shows carbonyl bands at 5·96 and 6·06 μ].

The base is very sparingly soluble, except in chloroform and boiling 2-ethoxyethanol; its salts, however, are very soluble in hydrophilic solvents, and even to some extent in chloroform. An *acid hydrochloride* was obtained by the passage of dry hydrogen chloride through a suspension of the base in dry ether. It was recrystallised with difficulty from ethanol–ether (1 : 19), then having m. p. 224—227° (Found: C, 61·0; H, 6·0; Cl, 13·6. $C_{25}H_{27}O_5N,2HCl$ requires C, 60·8; H, 5·9; Cl, 14·5%). The *picrate* was obtained by adding alcoholic picric acid to an alcoholic solution of the hydrochloride, as elongated plates, m. p. 208—212° (from 1 : 1 ethanol–2-ethoxyethanol) (Found: C, 57·2; H, 4·6; N, 8·6. $C_{31}H_{30}O_{12}N_4$ requires C, 57·2; H, 4·6; N, 8·6%).

The *dioxime* was obtained as colourless rhombohedra, m. p. 222°, from ethanol (Found : C, 66·7; H, 6·2; N, 9·2. $C_{25}H_{29}O_5N_3$ requires C, 66·6; H, 6·3; N, 9·3%). The *p*-nitro- and 2 : 4-dinitro-phenylhydrazone were amorphous. No other product of catalytic reduction of the thebaine–*p*-benzoquinone adduct could be isolated.

Tetrahydro-derivative (VI) *of the Thebaine–*p*-Benzoquinone Adduct.*—The 5′ : 6′-dihydro-compound (V) (5 g.), sodium borohydride (1 g.), and ethanol (50 ml.) were heated together under reflux until all the reactants dissolved, then for a further 90 min., and the mixture allowed to cool slowly to room temperature, whereafter the colourless crystals were collected and recrystallised from ethanol. The *tetrahydro-compound* was thus obtained as needles, m. p. 335° (Found : C, 70·5; H, 6·9. $C_{25}H_{29}O_5N$ requires C, 70·8; H, 6·9%). The infrared spectrum of this base showed a strong OH band at 2·85 μ and a strong band for saturated CO (at 5·88 μ).

Attempted Addition of cyclo*Pentadiene to the Thebaine–*p*-Benzoquinone Adduct.*—A solution of this adduct (2 g.) and *cyclo*pentadiene (4 g.) in chloroform (15 ml.) was set aside for 7 days. The white crystals that separated were the thebaine–quinol adduct, white needles (from ethanol), m. p. and mixed m. p. 224° (decomp.) (Found : C, 71·4; H, 6·0. Calc. for $C_{25}H_{25}O_5N$: C, 71·6; H, 6·0%).

Thebaine–Diethyl Maleate Adduct (Schöpf, von Gottberg, and Petri [2]).—It was found advantageous to heat the esterification mixture under reflux for 6 hr. instead of keeping it at room temperature for 5 days as recommended.[2] The ester was obtained as colourless prisms, m. p. 150·5° (lit., 151°), from ethanol.

*Thebaine–But-2-ene-*1 : 4*-diol "Adduct"* (VII; R = CH_2·OH).—Powdered lithium aluminium hydride (0·86 g.) in dry ether (350 ml.) was heated under reflux for 2 hr. with vigorous stirring (mercury seal) and the ester adduct (20 g.) was extracted from the Soxhlet apparatus directly into the hydride solution. After continuous extraction for 5 hr. all the ester was removed and the mixture was then stirred and heated under reflux for a further hour, then cooled and very cautiously added to 20% aqueous potassium hydroxide (500 ml.). The ether was removed and the aqueous layer extracted with chloroform (3 × 100 ml.). The combined ether and chloroform solutions were dried and evaporated, leaving an oil that crystallised on trituration with moist ether. The *but-2-ene-*1 : 4*-diol "adduct"* was collected and recrystallised from moist ether as colourless prisms, m. p. 108° (sintering at 98°), $[\alpha]_D^{18}$ −129° (*c* 1 in $CHCl_3$) (Found : C, 65·8, 65·9; H, 7·4, 7·6; N, 3·3, 3·4; H_2O, 4·3, 4·5. $C_{25}H_{29}O_5N,H_2O$ requires C, 66·2; H, 7·4; N, 3·3; H_2O, 4·3%). The *picrate* was prepared in and recrystallised from ethanol, as yellow prisms, m. p. 216—220° (decomp.) (Found : C, 55·4; H, 5·8; N, 8·1; loss at 150°, 5·8. $C_{29}H_{32}O_{12}N_4,C_2H_5$·OH requires C, 55·3; H, 5·7; N, 8·3; C_2H_5·OH, 5·9%).

Attempted catalytic reduction of the base over palladised charcoal afforded elongated plates, m. p. 119—123°, that nevertheless were identified by analysis and by the infrared spectrum as unreduced base monohydrate.

Thebaine–Diethyl Fumarate Adduct.—Thebaine (10 g.) and fumaryl chloride (5 g.) were warmed together in benzene (100 ml.), a deep violet colour developing. Ethyl alcohol was finally added. Colourless prisms separated very slowly and were found to consist of the hydrochloride of a base, presumably the adduct as no colour was observed on dissolving the substance in concentrated hydrochloric acid. The yields were very erratic and the substance could not be obtained analytically pure.

The Thebaine–Naphthaquinol Adduct.—Thebaine (2 g.) and 1 : 4-naphthaquinone (1 g.) were heated in ethanol (20 ml.) for 10 min. on the water-bath. Only a brown amorphous powder was obtained which could not be crystallised from ethanol or methanol (contrast Sandermann [1]). The powder was heated with dilute acetic acid for 5 min., the solution cooled, and the reddish crystals were collected. On recrystallisation from ethanol the *adduct* was obtained as colourless needles, m. p. 224° (decomp.) (Found : C, 74·0; H, 6·0; N, 2·6. $C_{29}H_{27}O_5N$ requires C, 74·2; H, 5·8; N, 2·9%).

*Thebaine Methiodide–*1 : 4*-Naphthaquinone Adduct.*—Thebaine methiodide (1 g.) and 1 : 4-naphthaquinone (0·4 g.) were warmed in chloroform (10 ml.). A red colour immediately developed and after 5 min. and rubbing with a glass rod produced pale orange crystals. When washed with aqueous acetone and dried, this *adduct* formed pale orange prisms, m. p. 193° (Found : C, 58·6; H, 4·7; N, 2·5; I, 21·9. $C_{29}H_{27}O_5N$,MeI requires C, 58·9; H, 4·95; N, 2·3; I, 20·9%). Repeated recrystallisation from ethanol gave only thebaine methiodide, m. p. and mixed m. p. 224°.

Attempted Rearrangement of the Thebaine–Maleic Anhydride Adduct.—The adduct (2 g.) was heated with concentrated hydrochloric acid (20 ml.) on the water-bath for 3 hr. On evaporation an acid- and alkali-soluble brown glass was obtained. That this was the thebaine–maleic acid

" adduct " was confirmed by esterification, which gave the diethyl ester, m. p. and mixed m. p. 150°. The same result was obtained when the maleic anhydride adduct was heated with glacial phosphoric acid at 170° for 15 min.

Attempted Addition of 1 : 2-*Naphthaquinone to Thebaine.*—Thebaine (2 g.) and the quinone (1 g.) were heated in nitrobenzene with a few crystals of quinol to prevent polymerisation. The mixture darkened and on removal of the nitrobenzene only a tar was obtained. Reaction in toluene or chloroform gave a red solution from which only thebaine could be recovered, and in ethanol only an amorphous brown solid. This last, when warmed with dilute acetic acid and subsequently neutralised with ammonia, gave an amorphous green precipitate.

Attempted Reaction of β-*Ethylthiocodide with* p-*Benzoquinone.*—β-Ethylthiocodide (m. p. 143°) was heated, in separate experiments, in benzene, toluene, and chloroform with *p*-benzoquinone, to give in each case a red solution from which only tar could be recovered. Reaction with maleic anhydride gave a yellow solution from which only maleic acid was recovered.

We thank Dr. F. B. Strauss and Mr. F. H. L. H. Hastings for the infrared measurements, and Dr. A. C. White and Mr. A. F. Green and the Wellcome Research Laboratories for the pharmacological tests reported above.

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366. *iso*Cyano-complexes of Rhodium.* Part I. *Tetraisocyanorhodium*(I) *Salts.*

By L. MALATESTA and (MISS) L. VALLARINO.

The preparation of rhodium(I) *iso*cyanide complexes, $[(R{\cdot}NC)_4Rh]X$ (where R = *p*-tolyl, *p*-chlorophenyl, or *p*-methoxyphenyl; X = chloride, perchlorate, or hexafluorophosphate), from hydrated rhodium trichloride and an excess of the *iso*cyanide is described. All the compounds prepared are diamagnetic and give conducting solutions in nitrobenzene. These complexes form addition compounds of different colours with water, alcohols, and chloroform.

*iso*CYANIDE complexes * of chromium [1], molybdenum [2], tungsten [3], manganese [4], iron [5], ruthenium [6], cobalt [7], nickel [8], palladium [9], copper, silver, and gold [10] have been prepared in these laboratories and this study has now been extended to rhodium. Also stable *iso*cyanide complexes of Co(I), in addition to those of Co(II) and Co(III), have been obtained.

In view of the analogy of complex-chemical behaviour between cobalt and rhodium, the existence of stable *iso*cyanide complexes of rhodium(I) could be predicted. These compounds have now been isolated.

The best method of preparation consists in treating an alcoholic solution of a rhodium compound, in the lowest possible oxidation state, with an alcoholic solution of an *iso*-cyanide. The most convenient starting material is hydrated rhodium trichloride. The action of *p*-chlorophenyl *iso*cyanide on rhodium trichloride leads to the isolation of a stable,

* *iso*Cyanide is I.U.P.A.C. nomenclature (cf. *J.*, 1952, 5069, rule 38), though these compounds have been termed *iso*nitriles in related papers.

[1] Malatesta, *Gazzetta*, 1952, **82**, 516; Malatesta and Sacco, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1952, **8**, (xii), 308.
[2] Malatesta, Sacco, and Gabaglio, *Gazzetta*, 1952, **82**, 548.
[3] Malatesta and Sacco, *Ann. Chim.* (*Italy*), 1953, **43**, 622.
[4] Sacco, *Gazzetta*, in the press; Sacco and Naldini, *ibid.*, in the press.
[5] Malatesta, *ibid.*, 1947, **77**, 240; Malatesta, Sacco, and Padoa, *Ann. Chim.* (*Italy*), 1953, **43**, 617; Malatesta and Sacco, *Z. anorg. Chem.*, 1953, **274**, 342; Malatesta, *Gazzetta*, 1953, **83**, 958.
[6] Malatesta, Padoa, and Sonz, *ibid.*, 1955, **85**, 1111.
[7] Malatesta and Sacco, *Z. anorg. Chem.*, 1953, **273**, 247; Malatesta, *Gazzetta*, 1953, **83**, 958, 499, 632; Malatesta and Sacco, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.* 1953, **8**, (xv), 93; Sacco, *ibid.*, p. 82.
[8] Malatesta and Sacco, *ibid.*, 1951, **6**, (xi), 379.
[9] Malatesta, *J.*, 1955, 3924.
[10] Sacco, *Gazzetta*, in the press; Sacco and Freni, *ibid.*, in the press.

crystalline, violet $[(p\text{-Cl}\cdot C_6H_4\cdot NC)_4Rh]Cl$, which is diamagnetic and gives a conducting solution in nitrobenzene. The action of other *iso*cyanides (phenyl, *p*-tolyl, and *p*-methoxyphenyl) on rhodium trichloride gives brown solutions which slowly become first green, and then violet, but do not give crystalline precipitates. Precipitation occurs on addition of anions such as perchlorate and hexafluorophosphate with formation of crystalline $[(p\text{-MeO}\cdot C_6H_4\cdot NC)_4Rh][PF_6]$, $[(p\text{-MeO}\cdot C_6H_4\cdot NC)_4Rh]ClO_4$, and $[(p\text{-Me}\cdot C_6H_4\cdot NC)_4Rh]ClO_4$, which behave analogously to $[(p\text{-Cl}\cdot C_6H_4\cdot NC)_4Rh]Cl$.

The above experiments confirm the formulation of these compounds as tetra*iso*cyanorhodium salts.

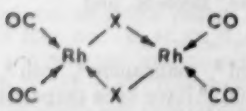
Rhodium(I)–*iso*cyanide complexes can also be obtained by treating $(CO)_4Rh_2Cl_2$ with the stoicheiometric amount of *iso*cyanide. They give crystals of different appearance, colour, and solubility, containing one molecule of solvent of crystallisation. The colour of these crystals varies greatly with the added molecule (see Table), but salts with different *iso*cyanides and different anions have similar colour when recrystallised from the same solvent. This can be taken to indicate that the solvent molecules are interacting within the co-ordination sphere, and the compounds are not clathrates, which, in turn, is an indication that the $[(R\cdot NC)_4Rh]^+$ ion is co-ordinatively unsaturated.

Colour of products obtained from various solvents.

Complex	Solvent: Benzene	Methanol	Ethanol	Aq. methanol	Chloroform
$[(p\text{-MeO}\cdot C_6H_4\cdot NC)_4Rh]ClO_4$	Green	Orange	Red	†	Violet
$[(p\text{-MeO}\cdot C_6H_4\cdot NC)_4Rh]PF_6$	Green	Violet	Red-violet	Red	Violet
$[(p\text{-Me}\cdot C_6H_4\cdot NC)_4Rh]ClO_4$	Yellow	Blue	Violet	Red	Violet
$[(p\text{-Cl}\cdot C_6H_4\cdot NC)_4Rh]Cl$	*	Light blue	Violet	†	Violet

* Too insoluble in benzene to be recrystallised. † Decomposed by this solvent.

The fact that rhodium(I), unlike cobalt(I) and manganese(I), does not give a compound with an effective atomic number corresponding to that of the next inert gas is not surprising. Rhodium(I) is isoelectronic with palladium(II), and the latter gives almost exclusively tetraco-ordinated complexes with square planar configuration and dsp^2 hybridisation.



The only well-established rhodium(I) complexes, $(CO)_4Rh_2X_2$ (X = Cl, Br, I),[12] have almost certainly the tetraco-ordinated structure shown in the inset. The formation of the π-type bonds between the filled 4*d* orbitals of the rhodium atom and the p_π orbitals on the carbon of the *iso*cyanide molecule will enhance the electron affinity of the metal and facilitate the attachment of a suitable solvent molecule by the vacant $5p_z$ orbital on the rhodium atom. This would explain the strong tendency of rhodium(I)–*iso*cyanide complexes to form solvates.

Experimental

p-Methoxyphenyl, *p*-tolyl, and *p*-chlorophenyl *iso*cyanides were prepared, purified, and analysed as described by Malatesta.[11] The alcohol-soluble rhodium trichloride was prepared as follows: powdered metallic rhodium mixed with four parts, by weight, of sodium chloride was heated for 2 hr. at 600—700° in a stream of dry chlorine. The mass thus obtained was extracted with hot water, affording a red solution of Na_3RhCl_6. This was made faintly alkaline with sodium hydroxide, and the precipitate of gelatinous yellow-brown rhodium(III) hydroxide was washed free from alkali and dissolved in hydrochloric acid. The solution was then taken to dryness. The red residue, consisting of $RhCl_3,xH_2O$ and a small amount of Na_3RhCl_6, was dissolved in anhydrous ethanol, which dissolves only the former. This solution is stable in the cold for some time, but on long standing or warming it deposits metallic rhodium as a black powder.

Tetra-p-chlorophenylisocyanorhodium Chloride.—Excess of the *iso*cyanide (5—6 mol. per atom of rhodium) was gradually added with gentle warming to an alcoholic solution of rhodium trichloride. A brown gelatinous precipitate was formed; this became first black and then brown, and on prolonged boiling with excess of *iso*cyanide became crystalline and violet. This

[11] Malatesta, *Gazzetta*, 1947, **77**, 238.
[12] Hieber and Lagally, *Z. anorg. Chem.*, 1943, **251**, 98.

violet product is insoluble in ether, benzene, chloroform, and methylene chloride. It is moderately soluble in boiling anhydrous methanol, from which it separates on cooling in a different crystal form and blue colour. This blue product, which is moderately soluble in methylene chloride and chloroform, can be reconverted into the violet form by prolonged boiling with ethanol. Both products are diamagnetic and electrolytes in nitrobenzene solution. The blue *solvate* (from methanol) (Found: Rh, 14·2; Cl, 24·7; N, 8·0. $C_{23}H_{16}N_4Cl_5Rh,CH_4O$ requires Rh, 14·3; Cl, 24·65; N, 8·0%) had m. p. 140° (decomp.), $\chi_M = -50 \times 10^{-6}$, $\Lambda_\infty = 28$ ohm^{-1} cm.^{2} at 20° in nitrobenzene (these conditions apply to all later conductivity data). The violet *salt* (from ethanol) (Found: Rh, 14·6; Cl, 25·1; N, 8·25. $C_{23}H_{16}N_4Cl_5Rh$ requires Rh, 14·9; Cl, 25·7; N, 8·3%) had m. p. 137° (decomp.), $\chi_M = -35 \times 10^{-6}$, $\Lambda_\infty = 29$ ohm^{-1} cm.^{2}.

Both products can also be obtained as follows: A solution of $(CO)_4Rh_2Cl_2$ [12] in chloroform, cooled in ice-water, is treated with the stoicheiometric amount (or a slight excess) of *iso*cyanide in chloroform solution. Carbon monoxide is evolved and the solution becomes violet. The solution is taken to dryness under reduced pressure, and the residue, when boiled in ethanol or methanol, affords products identical with the foregoing.

Tetra-p-tolylisocyanorhodium Perchlorate.—When rhodium trichloride and the *iso*cyanide were treated as described above, a violet solution was obtained from which no crystalline product could be isolated, but on addition of alcoholic sodium perchlorate a crystalline violet product separated. This is extremely soluble in methylene chloride and chloroform, rather soluble in boiling methanol, and insoluble in all other solvents. A hot methanol solution deposits a crystalline blue product on cooling, but from methylene chloride, on addition of benzene or ethyl acetate, a pale-yellow salt is obtained. A red salt is obtained by adding a little water to a hot solution in anhydrous methanol. A chloroform solution on evaporating and cooling gives a red-violet product. The last two products change composition on drying. The yellow *salt* (from benzene or ethyl acetate) (Found: Rh, 15·5; Cl, 5·3; N, 8·5. $C_{32}H_{28}O_4N_4ClRh$ requires Rh, 15·35; Cl, 5·3; N, 8·3%), had m. p. 198° (decomp.), $\chi_M = -50 \times 10^{-6}$, $\Lambda_\infty = 30$ ohm^{-1} cm.^{2}. The violet *solvate* (from ethanol) (Found: Rh, 14·5; Cl, 5·15; N, 8·0. $C_{32}H_{28}O_4N_4ClRh,C_2H_6O$ requires Rh, 14·3; Cl, 4·9; N, 7·8%), m. p. 207° (decomp.), $\chi_M = -60 \times 10^{-6}$, $\Lambda_\infty = 31$ ohm^{-1} cm.^{2}. The blue *solvate* (from methanol) (Found: Rh, 14·7; Cl, 5·3; N, 8·1. $C_{32}H_{28}O_4N_4ClRh,CH_4O$ requires Rh, 14·6; Cl, 5·05; N, 8·0%) had m. p. 200° (decomp.), $\chi_M = -80 \times 10^{-6}$, $\Lambda_\infty = 31$ ohm^{-1} cm.^{2}. The products obtained from chloroform and aqueous methanol alter their composition on drying in a vacuum desiccator.

Tetra-p-methoxyphenylisocyanorhodium perchlorate was prepared analogously to the *p*-tolyl derivative. The green salt (from benzene) (Found: Rh, 13·9; Cl, 4·75; N, 7·8. $C_{32}H_{28}O_8N_4ClRh$ requires Rh, 14·0; Cl, 4·8; N, 7·6%) had m. p. 180° (decomp.) and was diamagnetic: $\Lambda_\infty = 30$ ohm.$^{-1}$ cm.^{2}. The other products, red (from ethanol), orange (from methanol), and violet (from chloroform), on drying *in vacuo* gave a diamagnetic brown product (Found: Rh, 13·9; N, 7·5%).

Tetra-*p*-methoxyphenyl*iso*cyanorhodium hexafluorophosphate was obtained by reaction between rhodium trichloride and the *iso*cyanide as described above and treating the violet solution thus obtained with ammonium hexafluorophosphate. A red precipitate was obtained which, on recrystallisation from various solvents, gave the following compounds: Brilliant green *salt* (from benzene) (Found: Rh, 13·0; P, 3·8; N, 7·4. $C_{32}H_{28}O_4N_4F_6PRh$ requires Rh, 13·2; P, 4·0; N, 7·2%), m. p. 230° (decomp.), $\chi_M = -90 \times 10^6$, $\Lambda_\infty = 28$ ohm^{-1} cm.^{2}. Red *hydrate* (from aqueous methanol) (Found: Rh, 13·0; P, 3·75; N, 7·0. $C_{32}H_{28}O_4N_4F_6PRh,H_2O$ requires Rh, 12·9; P, 3·9; N, 7·0%), m. p. 215° (decomp.), $\chi_M = -70 \times 10^{-6}$. Red-brown *solvate* (from methylene chloride and ethanol) (Found: Rh, 12·6; P, 4·0; N, 6·6; Cl, 0. $C_{32}H_{28}O_4N_4F_6PRh,C_2H_6O$ requires Rh, 12·4; P, 3·75; N, 6·8%), diamagnetic. Violet *solvate* (from chloroform) (Found: Rh, 11·6; P, 3·9; N, 6·2; Cl, 10·5. $C_{32}H_{28}O_4N_4F_6PRh,CHCl_3$ requires Rh, 11·45; P, 3·4; N, 6·2; Cl, 10·7%), m. p. 237° (decomp.), $\chi_M = -60 \times 10^{-6}$.

It was not possible to determine the molecular weight of any of these compounds because those solvents in which they are sufficiently soluble cause decomposition.

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367. *Thiazoles derived from Chrysean and* iso*Chrysean.*

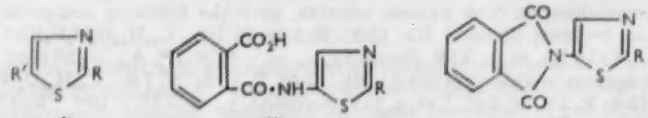
By A. Adams and R. Slack.

A number of derivatives of 5-amino- and 5-chloro-thiazole-2-carboxylic acids have been prepared from chrysean (5-amino-2-thiocarbamoylthiazole). *iso*Chrysean, an isomer isolated during the preparation of chrysean, has been identified as 5-amino-4-thiocarbamoylthiazole.

Chrysean was first prepared by Wallach [1] from hydrogen sulphide and a saturated solution of potassium cyanide. Hellsing [2] showed that the same compound could be obtained by treating thioformamide with aqueous potassium cyanide and that it was probably 5-amino-2-thiocarbamoylthiazole. More recently, Arnold and Scaife [3] have prepared 5-*p*-aminobenzenesulphonamidothiazole from chrysean and the structure was finally confirmed by Erlenmeyer and his co-workers.[4]

Although the yield of chrysean is poor (15—20%),[3] we have made numerous 1 kg. batches of crude product by passing hydrogen sulphide into ammoniated cyanide solution circulating through a packed tower. It has therefore been possible to prepare for biological examination a number of products—particularly carboxyhydrazides—derived from chrysean and to examine the chemistry of related thiazoles in some detail. The crude product melted at 204° but recrystallisation gave two isomers: one, m. p. 215—216°, which we consider to be the original chrysean; the other, which we have termed "*iso*-chrysean," m. p. 155° (cf. Ganapathi and Kulkarni [5]).

Chrysean is too fragile a molecule to permit normal degradation (cf. Arnold and Scaife [3]) and, although it is stabilised by acetylation or benzoylation, the acyl groups are resistant to subsequent hydrolysis. Protection of the amine group by conversion into a phthalimido-group which may be removed under mild, specific conditions has, however, proved advantageous. Chrysean (I; R = CS·NH$_2$, R′ = NH$_2$) with lead acetate gave 5-amino-2-cyanothiazole (I; R = CN, R′ = NH$_2$), but treatment of this with phthalic anhydride gave 5-*o*-carboxybenzamido-2-cyanothiazole (II; R = CN). Alkaline hydrolysis led to 5-*o*-carboxybenzamidothiazole-2-carboxylic acid (II; R = CO$_2$H) but attempts to convert this into the phthalimide by treatment with sulphuric acid were unsuccessful. Ring closure was effected with acetic acid but was accompanied by decarboxylation to 5-phthalimidothiazole (III; R = H). Excellent yields of 2-cyano-5-phthalimidothiazole (III; R = CN) were, however, obtained from the amino-nitrile and phthalic anhydride in boiling acetic acid. Acid-catalysed alcoholyses of this were not successful, but treatment of the corresponding ethyl imidoate with water gave ethyl 5-phthalimidothiazole-2-carboxylate



(I) (II) (III)

(III; R = CO$_2$Et). The protecting group was easily removed by treatment of the ester with hydrazine hydrate, the precise course of the reaction depending on the temperature and on the amount of hydrazine used. In boiling alcohol breakdown of the thiazole ring occurred, but the phthalimido-group was smoothly eliminated at room temperature. Excess of hydrazine hydrate gave the expected 5-aminothiazole-2-carboxyhydrazide (I; R = CO·NH·NH$_2$, R′ = NH$_2$), but two mols. of hydrazine gave ethyl 5-aminothiazole-2-carboxylate (I; R = CO$_2$Et, R′ = NH$_2$) and the hydrazine salt of phthalhydrazide.

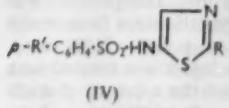
[1] Wallach, *Ber.*, 1874, **7**, 902.
[2] Hellsing, *Ber.*, (*a*) 1899, **32**, 1497; (*b*) 1900, **33**, 1774; (*c*) 1903, **36**, 3546.
[3] Arnold and Scaife, *J.*, 1944, 103.
[4] Erlenmeyer, Mengisen, and Prijs, *Helv. Chim. Acta*, 1947, **30**, 1865; Prijs, Mengisen, Fallab, and Erlenmeyer, *ibid.*, 1952, **35**, 187.
[5] Ganapathi and Kulkarni, *Proc. Indian Acad. Sci.*, 1953, **38**, *A*, 58.

The primary elimination of the phthalimide moiety from a bifunctional molecule of this nature is particularly interesting. With one mol. of hydrazine a mixture of the amino-ester and unchanged ethyl 5-phthalimidothiazole-2-carboxylate was produced.

Hellsing[2c] has prepared methyl 5-acetamidothiazole-2-carboxylate, m. p. 178°, from the silver salt of the corresponding acid. Repetition of this method gave only traces of product, but both the methyl (m. p. 216—217°) and the ethyl ester have now been prepared in good yields by hydrolysis of the methyl and the ethyl imidoate from 5-acetamido-2-cyanothiazole. Treatment of either ester with hydrazine hydrate gave 5-acetamidothiazole-2-carboxyhydrazide.

We also wished to examine the behaviour of the 5-amino-group towards diazotisation. Arnold and Scaife[3] reported that attempts to diazotise chrysean and 5-amino-2-cyanothiazole in the normal way gave highly coloured tars but they were able to diazotise the former by treating its solution in pyridine with nitrosyl chloride, and the latter by adding its aqueous solution to sodium nitrite and an excess of hydrochloric acid at 0°. We have confirmed these results but the dark red by-products which are obtained indicate that the diazonium compound couples with undiazotised material, even under acid conditions. The use of anhydrous conditions prevented self-coupling and 5-chloro-2-cyanothiazole (I; R = CN, R′ = Cl), together with varying amounts of 5-chlorothiazole-2-carboxyamide (I; R = CO·NH_2, R′ = Cl), was conveniently obtained from the amino-nitrile. The mixture from the Sandmeyer reaction was converted directly into 5-chlorothiazole-2-carboxylic acid (I; R = CO_2H, R′ = Cl) since both amide and nitrile were smoothly hydrolysed under alkaline conditions. The amide was also obtained from the nitrile by treatment with alcohol and dry hydrogen chloride, followed by hydrolysis. The acid, with diazomethane, gave methyl 5-chlorothiazole-2-carboxylate (I; R = CO_2Me, R′ = Cl), which with hydrazine hydrate gave 5-chlorothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = Cl). 5-Chloro-2-cyanothiazole reacted spontaneously with hydrazine hydrate to form 5-chlorothiazole-2-carboxyamidrazone [I; R = C(:NH)·NH·NH_2, R′ = Cl].

Thus, the reactivity of the 2-cyano-group is remarkably high (cf. 2-cyanothiazole ⟶ thiazole-2-carboxyamidrazone, Libman and Slack[6]) but we were none the less puzzled by the reported one-stage preparation of 5-*p*-aminobenzenesulphonamidothiazole (IV; R = H, R′ = NH_2), m. p. 185° (decomp.), from the corresponding acetamido-nitrile[3] (IV; R = CN, R′ = NHAc), a reaction which involves deacetylation, hydrolysis of the nitrile, *and decarboxylation*. In our opinion, the product of hydrolysis of both 5-*p*-acetamidobenzenesulphonamido-2-thiocarbamoylthiazole (IV; R = CS·NH_2, R′ = AcNH) and the nitrile is the carboxylic acid (IV; R = CO_2H, R′ = NH_2). This acid, which is decarboxylated under a variety of conditions (including recrystallisation), melts instantaneously in a bath at 150—160°, resolidifies, and remelts at *ca.* 190°. The monosodium salt (pH of 10% aqueous solution, 5—5·5) has also been prepared and the related 5-*p*-aminobenzenesulphonamido-2-thiocarbamoylthiazole (IV; R = CS·NH_2, R′ = NH_2) was made by reduction of the corresponding nitro-compound. For comparison with 5-*p*-aminobenzenesulphonamidothiazole-2-carboxylic acid (IV; R = CO_2H, R′ = NH_2), the analogous 4-carboxylic acid was prepared from ethyl 5-aminothiazole-4-carboxylate.[7]

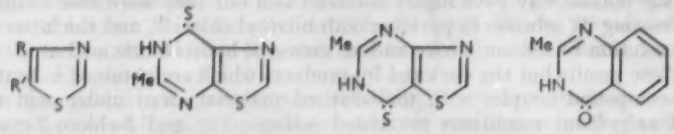


(IV)

We have also devoted particular attention to the elucidation of the structure of "*iso*chrysean," $C_4H_5N_3S_2$ (see p. 1870), which was isolated in almost 10% yield from crude chrysean by recrystallisation from dilute acetic acid and was purified by chromatography. It formed almost colourless needles, m. p. 155°; Ganapathi and Kulkarni[5] have also isolated an isomer, m. p. 146—146·5°, and maintain that it and chrysean yield the same acetyl derivative, softening at 214°, m. p. 236—237°, and that both give 5-acetamidothiazole on degradation. They conclude that chrysean exists in two stereoisomeric forms. In our hands, acetylation of chrysean with acetyl chloride in pyridine gave 5-acetamido-2-thiocarbamoylthiazole, m. p. 250°, and this yielded the same degradation products as were

[6] Libman and Slack, *J.*, 1956, in the press.
[7] Cook, Heilbron, and Levy, *J.*, 1947, 1594.

obtained by other workers. Acetylation of *iso*chrysean, however, gave a monoacetyl derivative, $C_6H_7ON_3S_2$, m. p. 208—210°, which indicated the presence of an amino-group but distinguished *iso*chrysean from chrysean. The acetyl compound with lead acetate gave lead sulphide and a nitrile, $C_6H_5ON_3S$, m. p. 202—204°. *iso*Chrysean was therefore an amino-thiocarbamoylthiazole and has now been identified as 5-amino-4-thiocarbamoylthiazole, a *position* isomer of chrysean, by the following reactions. Acetyl*iso*chrysean with warm dilute sodium hydroxide solution gave a weakly acidic yellow product, $C_6H_5N_3S_2$, formed by the loss of the elements of water. This elimination strongly suggested that the amino- and the thiocarbamoyl-group were adjacent and that the product was a thiazolopyrimidine (VI or VII) derived from [V; (*a*) R = CS·NH_2, R′ = NHAc, or (*b*) *vice versa*] [*cf.* the formation of 2-methyl-4-quinazolone (VIII) from *o*-acetamidobenzamide [8]].



(V) (VI) (VII) (VIII)

Now 5-aminothiazole-4-carboxyamide (V; R = CO·NH_2, R′ = NH_2) has been prepared by Cook, Heilbron, and Smith [9] and this, with acetyl chloride, gave a monoacetyl derivative, m. p. 212—213° (V; R = CO·NH_2, R′ = NHAc). The acetamidocyanothiazole from *iso*chrysean, with hydrogen peroxide in dilute alkali, was smoothly converted into the same compound (identical m. p., mixed m. p., and ultraviolet spectra), and the parent thioamide, therefore, is represented by (V; R = CS·NH_2, R′ = NH_2). Some other derivatives of *iso*chrysean have also been studied. Thus, with phthalic anhydride, 5-*o*-carboxybenzamido-4-thiocarbamoylthiazole (V; R = CS·NH_2, R′ = NH·CO·C_6H_4·CO_2H-*o*) was obtained and this was converted into the 4-nitrile by treatment with lead salts and alkali. The nitrile gave the corresponding amide on alkaline hydrolysis and the cyano-phthalimidothiazole [V; R = CN, R′ = $C_6H_4(CO)_2N$] with acetic anhydride.

Experimental

Chrysean (I; R = CS·NH_2, R′ = NH_2) *and* iso*Chrysean* (V; R = CS·NH_2, R′ = NH_2).—A solution of sodium cyanide (25 kg.) in water (57 l.) and aqueous ammonia (*d* 0·88; 1 l.) was circulated through a tower (consisting of a 5′ × 6″ "Pyrex" pipeline packed with 1″ Raschig rings) and was treated with hydrogen sulphide (15—16 kg.) during 6 hr. The product was washed with water and dried at 100° (1312 g.; m. p. 201—204°). Crystallisation from water (25 l.) and acetic acid (3·15 l.) (charcoal, 100 g.) gave chrysean (920 g.; m. p. 210—212°; m. p. 215—216° after further crystallisation from N-acetic acid). The mother-liquor was treated with ammonia (to pH 6), concentrated to 6·3 l. under reduced pressure, and the mixture of crude *iso*chrysean and ammonium acetate collected and washed with water. Crystallisation of the residue from ethanol gave *iso*chrysean (20·7 g.; m. p. 131—150°). The aqueous filtrate (6·3 l.) was continuously extracted with ether for two days. Evaporation of the ether gave an acetic acid solution which was diluted with three times its bulk of water, and was cooled overnight at 0°. Filtration gave a second crop of *iso*chrysean (86·5 g.; m. p. 131—160°). The filtrate was adjusted to pH 7 by the addition of ammonia solution and was set aside overnight at 0°, to give *iso*chrysean (20·2 g.; m. p. 136—160°). Crude *iso*chrysean (50 g.) in acetone (250 c.c.) was adsorbed on a column of activated alumina (1600 g.) prepared in chloroform suspension in 3″ "Pyrex" pipeline. The product was eluted with chloroform, fractions of 600 c.c. being collected and evaporated to dryness. Fractions 1—11 (35 g.), recrystallised from ethanol, gave *iso*chrysean in pale yellow needles (26 g.), m. p. 150—155°. Further recrystallisation gave *iso*chrysean (*5-amino-4-thiocarbamoylthiazole*) in almost colourless needles, m. p. 155° (Found: C, 30·8; H, 3·5; N, 26·5; S, 40·2. $C_6H_5N_3S_2$ requires C, 30·2; H, 3·2; N, 26·4; S, 40·3%).

5-Acetamido-2-thiocarbamoylthiazole.—A solution of chrysean (1·0 g.) in pyridine (4 c.c.) was treated at 0—5° with acetyl chloride (0·55 g.) to give 5-acetamido-2-thiocarbamoylthiazole

[8] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1948, **70**, 2423.
[9] Cook, Heilbron, and Smith, *J.*, 1949, 1440.

(0·8 g.) as yellow needles, m. p. 250° (decomp.), from 2N-acetic acid (Found : C, 36·0; H, 4·0; N, 21·1; S, 31·9. Calc. for $C_6H_7ON_3S_2$: C, 35·8; H, 3·5; N, 20·9; S, 31·9%).

5-Benzamido-2-cyanothiazole was obtained from 5-amino-2-cyanothiazole (Arnold and Scaife [3]) and benzoyl chloride in pyridine at 5°. Dissolution in dilute ammonia solution (charcoal), reprecipitation, and crystallisation from ethanol gave the *nitrile* as colourless needles, m. p. 211—212° (Found : N, 18·4; S, 14·4. $C_{11}H_7ON_3S$ requires N, 18·3; S, 14·0%).

5-Benzamidothiazole-2-carboxylic Acid.—A solution of 5-benzamido-2-cyanothiazole (1·0 g.) in 20% aqueous sodium hydroxide (20 c.c.) was boiled under reflux for 3 hr. Acidification of the cold solution gave *5-benzamidothiazole-2-carboxylic acid* (0·4 g.) which was dissolved in N-aqueous ammonia (charcoal) and reprecipitated by acidification, then having m. p. 159° (Found : N, 11·4; S, 12·8. $C_{11}H_8O_3N_2S$ requires N, 11·3; S, 12·9%).

5-o-Carboxybenzamido-2-cyanothiazole (II; R = CN).—Chlorobenzene was slowly distilled from a mixture of 5-amino-2-cyanothiazole (1 g.), phthalic anhydride (1·4 g.), and chlorobenzene (20 c.c.), fresh solvent being added to keep the volume constant. After 1 hr., the product was collected, washed with chlorobenzene, and dried at 100° (1·45 g.). *5-o-Carboxybenzamido-2-cyanothiazole* crystallised from methanol in pale yellow needles, m. p. 253°, or at 210° (decomp.) when placed into a pre-heated bath (Found : N, 15·1; S, 12·0. $C_{12}H_7O_3N_3S$ requires N, 15·4; S, 11·7%).

5-o-Carboxybenzamidothiazole-2-carboxylic Acid (II; R = CO_2H).—*5-o*-Carboxybenzamido-2-cyanothiazole (1 g.) was boiled with 2N-sodium hydroxide (10 c.c.) for 1 hr. Acidification of the cold, filtered solution gave the crude *acid* (0·9 g.) which, purified by dissolution in dilute ammonia (charcoal) and precipitation with dilute aqueous hydrochloric acid, had m. p. 154° (decomp.) (Found : C, 49·3; H, 2·2; N, 9·6; S, 11·65. $C_{12}H_8O_5N_2S$ requires C, 49·3; H, 2·8; N, 9·6; S, 11·0%).

5-Phthalimidothiazole (III; R = H).—*5-o*-Carboxybenzamidothiazole-2-carboxylic acid (1·0 g.) was boiled with acetic acid (15 c.c.) for 1 hr. The cooled solution deposited pale yellow needles (0·15 g.; m. p. 147—148°), and treatment of the filtrate with water gave further material (0·35 g., m. p. 141—143°). Recrystallisation from aqueous acetic acid gave 5-phthalimidothiazole, m. p. 147° (Found : N, 12·35; S, 14·2. Calc. for $C_{11}H_6O_2N_2S$: N, 12·2; S, 13·9%).

2-Cyano-5-phthalimidothiazole (III; R = CN).—5-Amino-2-cyanothiazole (10 g.) and powdered phthalic anhydride (16·5 g.) were heated under reflux in acetic acid (150 c.c.) for 6 hr. The *2-cyano-5-phthalimidothiazole* (18·4 g.) which separated was recrystallised from acetic acid to give orange needles, m. p. 255—256° (Found : N, 16·1; S, 12·6. $C_{12}H_5O_2N_3S$ requires N, 16·5; S, 12·6%).

Ethyl 5-Phthalimidothiazole-2-carboxylate (III; R = CO_2Et).—A stirred suspension of 2-cyano-5-phthalimidothiazole (50·0 g.) in dry chloroform (825 c.c.) and dry ethanol (20 g.) was saturated at 0—5° with dry hydrogen chloride. The stoppered flask was kept at 0° for 5 days. The mixture was filtered, and the residue was heated on the steam-bath with water (2 l.) for 1 hr. The flocculent product (49·1 g.), crystallised from light petroleum (b. p. 80—100°, 24 l.) (residue of substantially unchanged nitrile, 14·8 g.), gave pale yellow needles (28·4 g.), m. p. 162—165°. Alternate recrystallisation from light petroleum (b. p. 80—100°) and ethanol gave *ethyl 5-phthalimidothiazole-2-carboxylate* as pale yellow needles, m. p. 171° (Found : C, 55·7; H, 3·6; N, 9·3; S, 10·3. $C_{14}H_{10}O_4N_2S$ requires C, 55·6; H, 3·3; N, 9·3; S, 10·6%). Concentration of the chloroform–alcohol filtrate gave unchanged 2-cyano-5-phthalimidothiazole (1·2 g.).

5-Aminothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = NH_2).—The yellow solution formed by stirring hydrazine hydrate (100%; 90 c.c.) into a suspension of ethyl 5-phthalimidothiazole-2-carboxylate (58 g.) in ethanol (850 c.c.) was filtered and set aside overnight. The matted needles were collected and washed with a little ethanol. The filtrate and washings, concentrated to small bulk under reduced pressure at room temperature, gave yellow prisms [6·0 g.; m. p. 181—183° (decomp.)]. The needles (53·5 g.; m. p. 180—>360°) were dissolved in 2N-sodium hydroxide. Acidification of this solution gave phthalhydrazide (31·4 g.; m. p. 340—342°). The filtrate, made neutral with ammonia, deposited more crude amino-hydrazide [12·3 g.; m. p. 183—184° (decomp.)], and concentration of the mother-liquor under reduced pressure gave a further amount [1·7 g.; m. p. 181—182° (decomp.)]. The combined solids (20·0 g.) were recrystallised from water and then from ethanol, to give the *hydrazide*, m. p. 190° (decomp.) (Found : C, 30·4; H, 3·8; N, 34·6; S, 20·4. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8; N, 35·4; S, 20·3%).

Ethyl 5-Aminothiazole-2-carboxylate (I; R = CO_2Et, R′ = NH_2).—The solution formed by stirring hydrazine hydrate (100%; 3·53 g., 2 mol.) into a suspension of ethyl 5-phthalimidothiazole-2-carboxylate (10·65 g.; 1 mol.) in ethanol (160 c.c.) was filtered immediately. The filtrate,

from which yellow needles quickly separated, was set aside overnight. The solid was collected, and washed with a little ethanol. The filtrate and washings, evaporated to dryness under reduced pressure at room temperature, gave the crude ester as a yellow crystalline powder (4·0 g.; m. p. 117—118°). The needles (5·7 g.; m. p. >250°) were stirred with 2N-hydrochloric acid, phthalhydrazide (4·7 g.; m. p. 336—338°) was collected, and the filtrate was neutralised with ammonia and evaporated under reduced pressure to give a further small amount of crude ester (0·05 g.). The combined solids, recrystallised from water, gave *ethyl 5-aminothiazole-2-carboxylate* as cream-coloured needles, m. p. 118° (Found: C, 42·0; H, 4·8; N, 16·45; S, 19·0. $C_6H_8O_2N_2S$ requires C, 41·85; H, 4·7; N, 16·3; S, 18·6%).

n-Butyl 5-Phthalimidothiazole-2-carboxylate (III; R = CO_2Bu^n).—Prepared in 54% yield in the same manner as ethyl 5-phthalimidothiazole-2-carboxylate, the *n-butyl ester* crystallised (alternately from light petroleum and ethanol) as pale yellow needles, m. p. 167—169° (Found: C, 58·2; H, 4·4; N, 8·4; S, 9·5. $C_{16}H_{14}O_4N_2S$ requires C, 58·2; H, 4·3; N, 8·5; S, 9·7%).

n-Butyl 5-Aminothiazole-2-carboxylate (I; R = CO_2Bu^n, R′ = NH_2).—Prepared in 69% yield (cf. prep. of ethyl 5-aminothiazole-2-carboxylate), *n-butyl 5-aminothiazole-2-carboxylate* crystallised from 2N-acetic acid as fawn prisms, m. p. 81—82° (Found: C, 48·25; H, 6·0; N, 14·0; S, 16·4. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0; N, 14·0; S, 16·0%).

Ethyl 5-Acetamidothiazole-2-carboxylate.—A suspension of 5-acetamido-2-cyanothiazole [26] (10 g.) in dry chloroform (90 c.c.) and dry ethanol (30 c.c.) was saturated, at 0—5°, with dry hydrogen chloride. The stoppered flask was kept at 0° for two days, and the solid was collected and warmed with water (300 c.c.) for 15 min. The mixture was cooled and the residue (10·3 g.) crystallised from water, to give ethyl 5-acetamidothiazole-2-carboxylate as colourless needles, m. p. 191—192° (Found: N, 13·1. Calc. for $C_8H_{10}O_3N_2S$: N, 13·1%).

Methyl 5-acetamidothiazole-2-carboxylate (82%), m. p. 216—217°, was prepared as above (Found: C, 42·5; H, 4·0; N, 14·0; S, 16·4. Calc. for $C_7H_8O_3N_2S$: C, 42·0; H, 4·0; N, 14·0; S, 16·0%). Hellsing [26] gave m. p. 178° (decomp.).

5-Acetamidothiazole-2-carboxyhydrazide.—A mixture of hydrazine hydrate (100%; 2 c.c.), ethyl 5-acetamidothiazole-2-carboxylate (2 g.), and ethanol (25 c.c.) was heated at 100° for 15 min. and set aside overnight. The product (1·6 g.) recrystallised from ethanol to give cream-coloured *5-acetamidothiazole-2-carboxyhydrazide*, m. p. 286° (decomp.) (Found: C, 36·25; H, 4·3; N, 28·05; S, 16·35. $C_6H_8O_2N_4S$ requires C, 36·0; H, 4·0; N, 28·0; S, 16·0%). The hydrazide was also prepared similarly from the methyl ester.

5-Chloro-2-cyanothiazole (I; R = CN, R′ = Cl).—Freshly precipitated cuprous chloride (from 300 g. of $CuSO_4,5H_2O$) was dissolved in water (500 c.c.) and concentrated hydrochloric acid (375 c.c.). Dry, powdered sodium nitrite (9·4 g.) was added slowly, with stirring, to sulphuric acid (*d* 1·84; 63 c.c.), and the mixture was stirred at 65° until dissolution was complete. To this solution, at 0°, was added dropwise, with stirring, a cold solution of 5-amino-2-cyanothiazole (15·7 g.) in acetic acid (188 c.c.). The red syrup was stirred into a mixture of crushed ice (1500 g.), concentrated hydrochloric acid (180 c.c.), and cuprous chloride solution (210 c.c.), prepared as described above. After 16 hr., the brown copper complex was collected, washed with water, and dried at 100° (17·35 g.). Sublimation at 140—210°/0·1 mm. gave crude 5-chloro-2-cyanothiazole (5·75 g.). Resublimation at 60—100°/0·1 mm. gave colourless prisms (4·7 g.; m. p. 44—48°) and a pale yellow sublimate of the corresponding amide (0·2 g.; m. p. 175—180°) when the temp. was raised to 200°. Crystallisation of the low-melting product from light petroleum (b. p. 60—80°) gave *5-chloro-2-cyanothiazole* as colourless prisms, m. p. 50° (Found: N, 19·3; Cl, 24·4. C_4HN_2ClS requires N, 19·4; Cl, 24·5%). The crude amide, from ethanol, gave colourless needles, m. p. and mixed m. p. 189—191°.

5-Chlorothiazole-2-carboxyamide (I; R = CO·NH_2, R′ = Cl).—A solution of 5-chloro-2-cyanothiazole (2·0 g.) in dry chloroform (20 c.c.) and dry ethanol (1·5 c.c.) at 0—5°, saturated with dry hydrogen chloride, was set aside at 0° for 4 days. The colourless solid was warmed on the steam-bath with N-hydrochloric acid, triturated with aqueous sodium hydrogen carbonate, washed with water, and dried (0·47 g.; m. p. 190—193°). The chloroform filtrate, evaporated to dryness, gave a colourless residue which was treated in the same way (1·25 g.; m. p. 190—193°). Recrystallisation from ethanol gave *5-chlorothiazole-2-carboxyamide* in colourless needles, m. p. 193° (Found: N, 17·35. $C_4H_3ON_2ClS$ requires N, 17·2%). The amide was converted by boiling 2N-sodium hydroxide into 5-chlorothiazole-2-carboxylic acid.

5-Chlorothiazole-2-carboxylic Acid (I; R = CO_2H, R′ = Cl).—5-Chloro-2-cyanothiazole (4·25 g.) was treated for 1 hr. with boiling 2N-sodium hydroxide (40 c.c.). The crude product, which separated on cooling, was dissolved in hot water (30 c.c.) and reprecipitated with hydrochloric acid to give the *acid* (3·2 g.), m. p. 109° (decomp.). Acidification of the original alkaline

filtrate gave less pure material, m. p. 105° (decomp.) (0·95 g.). A sample, purified by repeated dissolution in 2N-sodium hydroxide (charcoal) and reprecipitation with 2N-hydrochloric acid, formed colourless needles, m. p. 111—112° (decomp.) (Found: N, 8·5. $C_4H_2O_2NClS$ requires N, 8·6%).

Methyl 5-chlorothiazole-2-carboxylate (I; R = CO_2Me, R′ = Cl) was prepared from 5-chlorothiazole-2-carboxylic acid (62·7 g.) and diazomethane (prepared from 150 g. of *N*-nitrosomethylurea) in dry ether (1600 c.c.) at 0—5°. The *ester* (46·6 g.), b. p. 76—80°/0·1 mm., solidified, and crystallisation from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 53° (Found: N, 8·0. $C_5H_4O_2NClS$ requires N, 7·9%).

5-Chlorothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = Cl).—Hydrazine hydrate (100%; 40 c.c.) in ethanol (250 c.c.) at 0°, and methyl 5-chlorothiazole-2-carboxylate (40·4 g.) in ethanol (250 c.c.), gave the crude *hydrazide* (37·9 g.). Recrystallisation from ethanol gave colourless needles, m. p. 197° (Found: N, 23·8; Cl, 20·2. $C_4H_4ON_3ClS$ requires N, 23·8; Cl, 20·1%).

5-Chlorothiazole-2-carboxyamidrazone [I; R = C(:NH)·NH·NH_2, R′ = Cl].—A mixture of 5-chloro-2-cyanothiazole (1·0 g.) and hydrazine hydrate (100%; 2 c.c.) gave, after 2 hr. at room temp., *5-chlorothiazole-2-carboxyamidrazone* (1·12 g.) which crystallised from ethanol as pale yellow needles, m. p. 148° (decomp.), resolidifying and re-melting at *ca.* 220° (Found: N, 31·25. $C_4H_5N_4ClS$ requires N, 31·7%).

(With Mrs. J. A. Murphy.) *5-p-Aminobenzenesulphonamidothiazole-2-carboxylic Acid* (IV; R = CO_2H; R′ = NH_2).—*5-p*-Acetamidobenzenesulphonamido-2-thiocarbamoylthiazole (45 g.) (Arnold and Scaife [3]) and 2N-sodium hydroxide were boiled under reflux for 1½ hr. The cooled solution was treated with ice and then acidified with 2N-hydrochloric acid to pH 1. The precipitate (27 g.) was dissolved in N-ammonia and stirred with charcoal during ½ hr. The filtered solution was adjusted to pH 1 by the addition of concentrated hydrochloric acid (no precipitation occurred at higher pH values) and the pale yellow solid was collected and dried. Dissolution in ethanol and addition of light petroleum (b. p. 60—80°) gave the product as an oil, which solidified, to give *5-p-aminobenzenesulphonamidothiazole-2-carboxylic acid* as a yellowish-white solid, m. p. 189° (decomp.),* decarboxylated at 124° if plunged into a bath from 110°. The acid was also decarboxylated in boiling water (Found: N, 14·25; S, 22·1. $C_{10}H_9O_4N_3S_2$ requires N, 14·0; S, 21·4%). The acid (24·0 g.), in cold dry methanol (240 c.c.), with sodium (1·84 g.) in dry methanol (120 c.c.) gave the yellow, crystalline *monosodium salt monomethanol solvate* (22·5 g.), decomp. by 200°. Precipitation was completed by the addition of a little dry ether. The salt was purified by solution in cold methanol and reprecipitation by the addition of dry ether (Found: N, 11·6; S, 18·4; Na, 6·15. $C_{10}H_8O_4N_3S_2Na,CH_3·OH$ requires N, 11·9; S, 18·1; Na, 6·5%. Loss *in vacuo* at 100° could not be determined accurately since dried material gained rapidly in wt. during weighing).

(With Mrs. J. A. Murphy.) *5-p-Aminobenzenesulphonamido-2-thiocarbamoylthiazole.*—*5-p*-Nitrobenzenesulphonamido-2-thiocarbamoylthiazole (10 g.) (Arnold and Scaife [3]) in N-ammonia (100 c.c.) was added with stirring to a boiling solution of ferrous sulphate (60 g.) in water (150 c.c.). The solution was made alkaline by the addition of aqueous ammonia (*d* 0·88), the mixture was boiled for 5 min., and again made alkaline. The solution was filtered (Hyflo), and the filtrate acidified to pH 4—5 with 2N-hydrochloric acid. The sulphonamide (8·5 g.) was dissolved in N-ammonia (100 c.c.) (charcoal) and reprecipitated (5 g.) by adjusting the pH to 4 with 2N-hydrochloric acid. Further purification was effected by dissolution in ethanol, and precipitation with light petroleum (b. p. 60—80°), and finally by recrystallisation from acetic acid, to give *5-p-aminobenzenesulphonamido-2-thiocarbamoylthiazole* as golden needles, m. p. 219—220° (Found: C, 38·3; H, 3·4; N, 17·7; S, 30·3. $C_{10}H_{10}O_2N_4S_3$ requires C, 38·1; H, 3·2; N, 17·8; S, 30·5%).

5-Acetamido-4-thiocarbamoylthiazole (V; R = CS·NH_2, R′ = NHAc).—*iso*Chrysean (6·0 g.) in dry pyridine (24 c.c.) was treated at 0—5° with acetyl chloride (3·7 g.). After 1 hr. at room temperature, the mixture was stirred into water (250 c.c.) and kept overnight. The yellow *5-acetamido-4-thiocarbamoylthiazole* (6·3 g.) crystallised from 2N-acetic acid as pale yellow needles, m. p. 208—210° (Found: C, 35·9; H, 3·6; N, 20·9; S, 32·1. $C_6H_7ON_3S_2$ requires C, 35·8; H, 3·5; N, 20·9; S, 31·9%).

5-Acetamido-4-cyanothiazole (V; R = CN, R′ = NHAc).—*Method* I. 5-Acetamido-4-thiocarbamoylthiazole (2·2 g.), lead acetate (4·2 g.), and water (20 c.c.) were boiled under reflux for ¾ hr. The hot solution was filtered and the black residue was extracted with boiling N-acetic

* This is the m. p. of the decarboxylated product *with which there is no depression on slow heating.*

acid (30 c.c.). This extract was added to the filtrate. The product separated in yellow needles (0·8 g.). Recrystallisation from N-acetic acid gave *5-acetamido-4-cyanothiazole* in almost colourless needles, m. p. 202° (Found: C, 43·4; H, 3·2; N, 25·5. $C_6H_4ON_3S$ requires C, 43·1; H, 3·0; N, 25·1%).

Method II. A concentrated aqueous solution of lead nitrate (3·3 g.) was treated with 10% aqueous sodium hydroxide until the precipitate redissolved. 5-Acetamido-4-thiocarbamoylthiazole (2·0 g.) was added, and the mixture was shaken overnight. Lead sulphide was removed and the filtrate slowly acidified (pH 4; critical) with 2N-hydrochloric acid, and set aside overnight. The solid (1·4 g.) on crystallisation from 2N-acetic acid (charcoal) gave faintly pink needles, m. p. 202—204°, not depressed on admixture with 5-acetamido-4-cyanothiazole.

1 : 6-*Dihydro-2-methyl-6-thiothiazolo*(4′ : 5′-5 : 4)*pyrimidine* (VI).—5-Acetamido-4-thiocarbamoylthiazole (1·0 g.) was treated with boiling 2N-sodium hydroxide (10 c.c.) for 90 min. The solution was treated at 0° with 2N-hydrochloric acid, to give the bright yellow anhydroderivative. This (0·65 g.) was purified by dissolution in 2N-sodium hydroxide (charcoal), followed by reprecipitation with aqueous hydrochloric acid. 1 : 6-*Dihydro-2-methyl-6-thiothiazolo*(4′ : 5′-5 : 4)*pyrimidine* was obtained as a yellow powder, m. p. 266°, soluble in aqueous sodium hydrogen carbonate, but not in dilute acid (Found: C, 39·7; H, 2·8; N, 22·8; S, 35·8. $C_6H_4N_3S_2$ requires C, 39·3; H, 2·75; N, 22·9; S, 35·0%).

5-Acetamidothiazole-4-carboxyamide (V; R = $CO{\cdot}NH_2$, R′ = NHAc).—*Method* I. A suspension of 5-acetamido-4-cyanothiazole (1 g.) in acetone (10 c.c.) was treated with 20% aqueous hydrogen peroxide (25 c.c.) and 2N-sodium carbonate (3 c.c.). The mixture was warmed on the steam-bath for 45 min., with the addition of further acetone as required to prevent the precipitation of the solid, and of aqueous hydrogen peroxide (20%; 1 c.c.) after 25 min. The colourless crystalline *amide* (0·8 g.) was collected after 16 hr. at room temperature. Crystallisation from water gave colourless needles, m. p. 212—213°. The m. p. was not depressed on admixture with an authentic sample and their light absorptions in methanol were identical [$\lambda_{max.}$ 282 mμ (log ε 4·15); $\lambda_{min.}$ 235 mμ (log ε 3·60); $\lambda_{inf.}$ 260 mμ (log ε 3·93)] (Found: C, 38·65; H, 3·95; N, 22·5; S, 17·5. $C_6H_7O_2N_3S$ requires C, 38·9; H, 3·8; N, 22·7; S, 17·3%).

Method II. A solution of 5-aminothiazole-4-carboxyamide (2·0 g.) (Cook *et al.*[9]) in dry pyridine (20 c.c.) was treated, at 0—5°, with acetyl chloride (1·5 g.). After 2 hr., water (150 c.c.) was added, and the solution was filtered from a little impurity and treated with concentrated hydrochloric acid to pH 6—7. The mixture was set aside for 2 hr., during which the product crystallised in almost colourless needles (1·9 g.). Recrystallisation from water gave the amide as colourless needles, m. p. 212—213°. The m. p. was not depressed on admixture with the specimen prepared from *iso*chrysean, and their light absorptions in methanol were identical.

5-o-Carboxybenzamido-4-thiocarbamoylthiazole.—*iso*Chrysean (10 g.), powdered phthalic anhydride (12·5 g.), and acetic acid (150 c.c.) were boiled under reflux for 2 hr., then kept overnight. The product (17·6 g.), crystallised from acetic acid, gave *5-o-carboxybenzamido-4-thiocarbamoylthiazole* as pale yellow needles, m. p. 243—244° (Found: C, 46·2; H, 3·1; N, 13·9. $C_{12}H_9O_3N_3S_2$ requires C, 46·9; H, 2·95; N, 13·7%).

5-o-Carboxybenzamido-4-cyanothiazole.—A concentrated aqueous solution of lead nitrate (2·65 g.) was treated with 2N-sodium hydroxide until the precipitate redissolved. *5-o*-Carboxybenzamido-4-thiocarbamoylthiazole (2·2 g.) was added, and the mixture was shaken overnight. The solution was filtered from lead sulphide and acidified with 2N-nitric acid. The product (1·8 g.) was purified by repeated dissolution in 2N-sodium hydroxide and reprecipitation with 2N-nitric acid, to give *5-o-carboxybenzamido-4-cyanothiazole* as a white powder, m. p. 224° (decomp.) (Found: C, 52·7; H, 2·8; N, 15·4; S, 12·0. $C_{12}H_7O_3N_3S$ requires C, 52·7; H, 2·6; N, 15·4; S, 11·7%). The use of a lead carbonate suspension instead of lead nitrate gave the nitrile in 96% yield.

5-o-Carboxybenzamidothiazole-4-carboxyamide.—*5-o*-Carboxybenzamido-4-cyanothiazole (7·9 g.) was boiled under reflux with 2N-sodium hydroxide (79 c.c.) for 2 hr. The cooled solution was filtered and acidified with 2N-hydrochloric acid to give the *phthalamic acid* (5·85 g.) which was purified by repeated dissolution in 2N-sodium hydroxide followed by reprecipitation with 2N-hydrochloric acid to give a white powder, m. p. 203° (decomp.), resolidifying to yellow rhombohedra, m. p. 345—350° (Found: C, 49·5; H, 3·1; N, 14·6; S, 11·25. $C_{12}H_9O_4N_3S$ requires C, 49·5; H, 3·1; N, 14·4; S, 11·0%).

4-Cyano-5-phthalimidothiazole.—A mixture of *5-o*-carboxybenzamido-4-cyanothiazole (11·0 g.) and acetic anhydride (50 c.c.) was boiled under reflux for 2 hr. The solution was

filtered (charcoal) and cooled, to give colourless prisms (6·45 g.) of the phthalimide, which were finally washed with acetic anhydride. Recrystallisation from acetic anhydride gave *4-cyano-5-phthalimidothiazole*, m. p. 196° (Found: C, 56·7; H, 2·2; N, 16·2. $C_{12}H_5O_2N_3S$ requires C, 56·5; H, 2·0; N, 16·5%).

5-p-Aminobenzenesulphonamidothiazole-4-carboxylic Acid.—A solution of ethyl 5-aminothiazole-4-carboxylate (50·5 g.) (Cook *et al.*[7]) in dry pyridine (505 c.c.) was treated at 0°, with stirring, with *p*-acetamidobenzenesulphonyl chloride (79 g.). The solution was set aside for 4 days, and was then poured on ice (2 kg.) and sufficient concentrated hydrochloric acid to keep the mixture acid. The product was hydrolysed by boiling with 2N-sodium hydroxide (1 l.) for 2 hr. The boiling solution was filtered (charcoal), cooled, and again filtered. Treatment with concentrated hydrochloric acid (ice-cooling) gave a sticky product (41·3 g.) which eventually crystallised. After being washed with very dilute hydrochloric acid and drying at 40° (41·3 g.), this was repeatedly dissolved in dilute ammonia (charcoal) and reprecipitated with dilute hydrochloric acid at 0°, to give *5-p-aminobenzenesulphonamidothiazole-4-carboxylic acid* in almost colourless needles, m. p. 184° (decomp.) on slow heating, but immediate decomp. in a bath at 160° (Found: C, 38·95; H, 3·2; N, 13·6; S, 21·1; loss in wt. at 100°, 3·2. $C_{10}H_9O_4N_3S_2,\frac{1}{2}H_2O$ requires C, 38·9; H, 3·3; N, 13·6; S, 20·8; H_2O, 2·9%).

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368. *Purines, Pyrimidines, and Glyoxalines. Part II.* New Syntheses of Some Pyrimidine Nucleosides.*

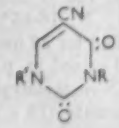
By R. K. RALPH and G. SHAW.

N-Cyanoacetyl-*N*-methylurethane (IV) has been prepared and converted into α-cyano-β-ethoxy-*N*-ethoxycarbonyl-*N*-methylacrylamide (I; R = Me). The latter compound with ammonia gave 5-cyano-3-methyluracil. Reaction of either of the ethoxy-acrylamides (I; R = H and Me) with a number of D-glycosylamines in water or alcohol gave the 5-cyano-1-D-glycopyranosyluracils (III; R = H, R′ = D-ribo-, D-xylo-, D-galacto-, D-gluco-, and 2-deoxy-D-gluco-pyranosyl) and the 3-methyl derivatives (III; R = Me, R′ = D-ribo-, D-xylo-, D-galacto- and D-gluco-pyranosyl) respectively.

IT was recorded in Part I* that reaction of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (I; R = H) with ammonia or with primary amines yields the 1-alkyl(aryl-)-5-cyanouracils (III; R = H, R′ = H, alkyl, or aryl). In these reactions, initially the linear amino-compounds (II; R = H) are formed and were separately isolated in the examples (II; R = H, R′ = Ph and Ph·NH).

$EtO{\cdot}CH{:}C(CN){\cdot}CO{\cdot}NR{\cdot}CO_2Et$ (I)

$R'{\cdot}NH{\cdot}CH{:}C(CN){\cdot}CO{\cdot}NR{\cdot}CO_2Et$ (II)



(III)

$NC{\cdot}CH_2{\cdot}CO{\cdot}NMe{\cdot}CO_2Et$ (IV)

The present work was undertaken in an attempt to widen the scope of these reactions to include the synthesis of 5-cyanouracils with substituents in position 3 (III; R′ = H) and jointly in positions 1 and 3, and at the same time to extend the reactions to include the synthesis of 5-cyano-1-glycosyluracils related to the naturally occurring pyrimidine nucleosides.

* Part I, *J.*, 1955, 1834.

Reaction of *N*-methylurethane with a mixture of cyanoacetic acid and acetic anhydride gave a readily separable mixture of *N*-acetyl- and *N*-cyanoacetyl-*N*-methylurethane (IV). The latter product reacted smoothly with ethyl orthoformate and acetic anhydride, to give an excellent yield of the ethoxy-compound (I; R = Me); the reaction of this with aqueous ammonia gave the pyrimidine (III; R = Me, R′ = H).

The preparation of 1-D-glycosyluracils by this method required D-glycosylamines (1-amino-1-deoxy-sugars or tautomers thereof) as intermediates, and, in particular, for the synthesis of uridine derivatives, 1-D-ribofuranosylamine. The literature records several D-glycosylamines including D-ribosylamine,[1] D-xylosylamine,[2] D-glucosylamine,[3] and D-galactosylamine,[2] generally prepared by reaction of the sugar with dry methanolic ammonia at room temperature for times varying from a few days for ribose, xylose, and galactose to about a month for glucose; in addition Muskat[4] claimed the preparation of D-glucosylamine by dissolving glucose in liquid ammonia, but this reaction was unsuccessful in the hands of Wayne and Adkins.[5]

Reaction of D-ribosylamine with (I; R = H) in aqueous or ethanolic solution[6] at room temperature or with gentle warming gave a solution which failed to give a precipitate with basic lead acetate; however, when the mildly alkaline solution was warmed for a short time and then cooled, an insoluble lead salt appeared. This behaviour suggests the formation of a linear compound (II; R = H, R′ = D-ribosyl) and subsequent cyclisation of this to a pyrimidine nucleoside. The lead salt was suspended in ethanol and decomposed with hydrogen sulphide, to give eventually a 40% yield of 5-cyano-1-D-ribopyranosyluracil (III; R = H, R′ = 1-D-ribopyranosyl). The pyranose nature of the compound was indicated by titration with sodium metaperiodate and the presence of a pyrimidine ring was shown by ultraviolet-absorption measurements. The specific rotation of the compound suggests that it is the β-form. Similarly the nucleosides (III; R = H, R′ = 1-D-xylo-, D-galacto-, D-gluco-, and 2-deoxy-2-D-gluco-pyranosyl) were prepared from the ester (I; R = H) and the corresponding amino-sugar.

Reaction of the glycosylamines with the ester (I; R = Me) proceeded readily in aqueous or ethanolic solution at room temperature, or with warming, to give directly, good yields of the nucleosides (III; R = Me, R′ = 1-D-ribo-, D-xylo-, D-galacto-, and D-gluco-pyranosyl).

Experimental

Absorption max. and $[\alpha]_D$ were measured in H_2O.

The D-glycosylamines were prepared by saturating a methanolic solution or suspension of the sugar with dry ammonia gas and allowing the solution so obtained to stand. Crystalline material was filtered off and used directly.

N-Cyanoacetyl-N-methylurethane.—A mixture of cyanoacetic acid (43 g.), *N*-methylurethane (52·2 g.), and acetic anhydride (102 g.) was heated on a water-bath for 3 hr., to give a reddish-brown solution, which was cooled and added to water (2 l.). The precipitated oil was extracted with ether (2 × 200 ml.), and the extract washed with water and aqueous sodium hydrogen carbonate until free from acid. The dried extract was evaporated to an oil (45 g.) which was distilled *in vacuo*, to give *N*-acetyl-*N*-methylurethane (20 g.), b. p. 81—83°/21 mm. (Found: C, 49·9; H, 7·75; N, 9·8. Calc. for $C_6H_{11}O_3N$: C, 49·65; H, 7·65; N, 9·65%), and *N-cyanoacetyl-N-methylurethane* (22·9 g.), b. p. 133°/1 mm. (Found: C, 49·05; H, 5·85; N, 16·55. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·95; N, 16·45%). The latter (0·26 g.) in ethanol (5 ml.) containing aniline (2—3 drops) was boiled for 30 min., cooled, and treated with water to precipitate cyanoacetanilide (0·1 g.), m. p. and mixed m. p. 198°.

α-Cyano-β-ethoxy-N-ethoxycarbonyl-N-methylacrylamide.—A mixture of *N*-cyanoacetyl-*N*-methylurethane (13 g.), ethyl orthoformate (13 g.), and acetic anhydride (25 ml.) was boiled under reflux for 1 hr., to give a pale brown solution which was distilled *in vacuo* to afford *α-cyano-β-ethoxy-N-ethoxycarbonyl-N-methylacrylamide* (14·3 g.), b. p. 160°/1 mm. (Found: C, 53·1; H, 6·55; N, 12·05. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·25; N, 12·3%).

[1] Levene and La Forge, *J. Biol. Chem.*, 1915, **20**, 440.
[2] Lobry de Bruyn and van Leent, *Rec. Trav. chim.*, 1895, **14**, 145.
[3] Irvine, Thomson, and Garrett, *J.*, 1913, **103**, 239; Levene, *J. Biol. Chem.*, 1916, **24**, 60.
[4] Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693.
[5] Wayne and Adkins, *ibid.*, 1940, **62**, 3314.
[6] For a note see Ralph and Shaw, *Chem. and Ind.*, 1955, **38**, 1185.

5-Cyano-3-methyluracil.—The foregoing acrylamide (0·63 g.) was shaken with aqueous ammonia (10 ml.; 3%), a clear solution being soon obtained. This was acidified with hydrochloric acid, cooled and set aside. The precipitated *5-cyano-3-methyluracil* (0·25 g.) crystallised from water as needles, m. p. 223° (Found: C, 47·8; H, 3·2; N, 27·65. $C_6H_5O_2N_3$ requires C, 47·7; H, 3·35; N, 27·8%).

5-Cyano-3-methyl-1-D-xylopyranosyluracil.—(*a*) A solution of the ethoxy-acrylamide (1·28 g.) in ethanol (10 ml.) was treated with D-xylosylamine (0·84 g.). The suspension was warmed and shaken, a clear solution being soon obtained. This was evaporated to about half volume and cooled; after a short time a jelly containing a few crystals separated; when rubbed, the gel rapidly crystallised. The solid was washed with a little ethanol and ether; *5-cyano-3-methyl-1-D-xylopyranosyluracil monohydrate* (0·8 g.) separated from ethanol as needles, m. p. 120° (decomp. to a glass, then m. p. 200°), $[\alpha]_D^{20}$ −17·2° (*c* 4·08) (Found: C, 44·3; H, 5·0; N, 14·15° $C_{11}H_{13}O_6N_3,H_2O$ requires C, 43·85; H, 5·0; N, 13·95%). Absorption max. at 273 (ε 11,580) and <215 mμ (ε > 10,100). A further quantity (0·25 g.) of the xyloside was recovered from the filtrate. In 24 hr. at 20° the substance consumed 2·04 mols. of 0·0841N-sodium metaperiodate and liberated 0·85 mol. of formic acid. (*b*) The ethoxy-acrylamide (0·48 g.) was covered with water (1 ml.), and D-xylosylamine (0·31 g.) was added. The mixture was shaken; after about 5 min. a clear very pale yellow solution was obtained. This was kept over phosphoric oxide to give finally a syrup which when stirred with ethanol and ether gave a crystalline solid (0·35 g.), m. p. and mixed m. p. 120° (decomp. to a glass; m. p. 200°).

5-Cyano-3-methyl-1-D-ribopyranosyluracil.—The ethoxy-acrylamide (1·15 g.) in ethanol (20 ml.) was treated with D-ribosylamine (0·74 g.); the mixture was gently warmed and shaken to give a clear solution; this was evaporated to *ca.* 5 ml. and cooled. A small portion was treated with ether, to precipitate a gum which when kept with a little ethanol gave crystals. The main solution, when seeded, rapidly crystallised. *5-Cyano-3-methyl-1-D-ribopyranosyluracil* (0·55 g.) separated from ethanol as needles, m. p. 223°, $[\alpha]_D^{20}$ −16·91° (*c* 2·36) (Found: C, 46·15; H, 4·55; N, 14·55. $C_{11}H_{13}O_6N_3$ requires C, 46·65; H, 4·65; N, 14·85%); a further quantity (0·53 g.) was obtained by treating the ethanol solution with ether. Absorption max. at 273 (ε 5780) and <215 mμ (ε > 5300). In 24 hr. at 20° the substance consumed 1·78 mols. of 0·0841N-sodium metaperiodate and liberated 1·2 mols. of formic acid.

5-Cyano-3-methyl-1-D-galactopyranosyluracil.—D-Galactosylamine (1·5 g.) was added to a solution of the ethoxy-acrylamide (1·9 g.) in ethanol (10 ml.); the suspension was warmed for a short time to give a clear solution which when cooled gave a crystalline precipitate; *5-cyano-3-methyl-1-D-galactopyranosyluracil* (1·78 g.) separated from ethanol as prisms, m. p. 240° (decomp.), $[\alpha]_D^{20}$ +42·2° (*c* 4·26) (Found: C, 45·95; H, 4·7; N, 13·5. $C_{12}H_{16}O_7N_3$ requires C, 46·0; H, 4·85; N, 13·4%). Absorption max. at 273 (ε 11,580) and <215 mμ (ε >10,300). In 24 hr. at 20° the substance consumed 2·3 mols. of 0·0826N-sodium metaperiodate and liberated 1·1 mols. of formic acid.

5-Cyano-3-methyl-1-D-glucopyranosyluracil.—D-Glucosylamine (1·25 g.), warmed with the ethoxy-acrylamide (1·62 g.) in ethanol (10 ml.) for a few min., gave a clear solution; this after 1 hr. was treated with ether, to precipitate a semi-solid gum. The solvent was decanted, the gum dissolved in ethanol (20 ml.), and the solution kept at 0° for a few hr. A crystalline precipitate was obtained; *5-cyano-3-methyl-1-D-glucopyranosyluracil monohydrate* (1·1 g.) crystallised from ethanol as prisms, m. p. 204° (after sintering at 135—140°), $[\alpha]_D^{20}$ +13·4° (*c* 4·10) (Found: C, 43·65; H, 5·15; N, 12·55. $C_{12}H_{15}O_7N_3,H_2O$ requires C, 43·5; H, 5·15; N, 12·7%). Absorption max. at 273 (ε 7800) and <215 mμ (ε > 10,300). In 24 hr. at 20° the substance consumed 1·91 mols. of 0·0826N-sodium metaperiodate and liberated 1·17 mols. of formic acid.

5-Cyano-1-D-ribopyranosyluracil.—A solution of D-ribosylamine (1·41 g.) in water (30 ml.) was added to one of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2 g.) in warm ethanol (30 ml.) and kept at room temperature for 1 hr. The solution was evaporated to dryness and the resulting gum dissolved in water (10 ml.) and treated with a solution of basic lead acetate; there was no immediate precipitate but when the solution was warmed on the steam-bath for a few minutes and then cooled a thick solid precipitate was obtained. The lead salt was filtered off, washed with a little ice water, suspended in ethanol, and decomposed with hydrogen sulphide. After removal of lead sulphide, the colourless solution was evaporated to a small volume and cooled. A crystalline precipitate was obtained. *5-Cyano-1-D-ribopyranosyluracil* (0·96 g.) separated from ethanol as needles, m. p. 231°, $[\alpha]_D^{20}$ −22·85° (*c* 7·26) (Found: C, 44·4; H, 4·1; N, 15·5. $C_{10}H_{11}O_6N_3$ requires C, 44·6; H, 4·1; N, 15·6%). Absorption max. at 274 (ε 6270) and <215 mμ (ε > 5500). In 24 hr. at 20° the substance consumed 2·1 mols. of 0·0841N-sodium metaperiodate and liberated 1·23 mols. of formic acid.

*5-Cyano-*1-D-*galactopyranosyluracil.*—D-Galactosylamine (1·75 g.) was added to α-cyano-β-ethoxycarbonylacrylamide (2·12 g.) in ethanol (15 ml.). The solution was warmed and shaken until clear. Addition of basic lead acetate to the alcoholic solution precipitated a solid. This was filtered off, washed with water, dispersed in ethanol, and decomposed with hydrogen sulphide. Lead sulphide was filtered off, and the colourless filtrate evaporated to a small volume, and set aside. A crystalline precipitate soon appeared; *5-cyano-*1-D-*galactopyranosyluracil* (0·6 g.) separated from ethanol as needles, m. p. 254°, $[\alpha]_D^{20}$ +50·2° (*c* 2·39) (Found: C, 43·9; H, 4·25; N, 13·95. $C_{11}H_{13}O_7N_3$ requires C, 44·15; H 4·4; N, 14·05%). Absorption max. at 274 (ε 4700) and <215 mμ (ε > 4650). In 24 hr. at 20° the substance consumed 2·0 mols. of 0·0826N-sodium metaperiodate and liberated 1·0 mol. of formic acid.

*5-Cyano-*1-D-*glucopyranosyluracil.*—A suspension of D-glucosylamine (1·79 g.) in ethanol (20 ml.) containing α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2·12 g.) was shaken and warmed gently, to give, after a short time, a clear solution. This was evaporated to dryness and the residual gum dissolved in water, and to the solution was added basic lead acetate until no further precipitate was obtained. The lead salt was filtered off, washed with water and ethanol, and decomposed in ethanol with hydrogen sulphide. Lead sulphide was filtered off and the colourless filtrate evaporated to a small volume and set aside overnight; a crystalline precipitate separated. *5-Cyano-*1-D-*glucopyranosyluracil* (0·61 g.) recrystallised from ethanol as needles, m. p. 240°, $[\alpha]_D^{20}$ +44·2° (*c* 1·81) (Found: C, 44·35; H, 4·4; N, 14·0%). Absorption max. at 274 (ε 9450) and <215 mμ (ε > 9200). In 24 hr. at 20° the substance consumed 1·9 mols. of 0·0826N-sodium metaperiodate and liberated 0·87 mol. of formic acid.

*5-Cyano-*1-D-*xylopyranosyluracil.*—(*A*) D-Xylosylamine (1·49 g.) was shaken with α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2·12 g.) in ethanol (20 ml.) until a solution was obtained. This was evaporated to a gum which was dissolved in water. Addition of basic lead acetate gave a precipitate which was filtered off, washed with water, and decomposed in ethanol with hydrogen sulphide. The solution was filtered from lead sulphide, evaporated to a small volume, and set aside, to give a crystalline precipitate; *5-cyano-*1-D-*xylopyranosyluracil* (0·41 g.) recrystallised from ethanol as needles, m. p. 247°, $[\alpha]_D^{20}$ −25·1° (*c* 2·38) (Found: C, 44·45; H, 4·05; N, 15·3%). Absorption max. at 273 (ε 11,090) and <215 mμ (ε > 10,650). In 24 hr. at 20° the substance consumed 1·86 mols. of 0·0826N-sodium metaperiodate and liberated 0·99 mol. of formic acid. (*B*) A finely powdered mixture of D-xylosylamine (0·5 g.) and α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (0·74 g.) was heated at 110° (bath) for 5 min. A clear melt was obtained which was cooled, dissolved in water, and worked up as under (*A*), to give the xyloside (0·1 g.), m. p. and mixed m. p. 247°. (*C*) D-Xylosylamine (1·49 g.) and the acrylamide (2·12 g.) were allowed to react in ethanol as in (*A*). The solution was treated with methanolic ammonia, to precipitate a colourless solid (presumably an ammonium salt). Crystallisation of this from ethanol gave however the xyloside (0·5 g.), m. p. and mixed m. p. 245°, $[\alpha]_D^{20}$ −24·9° (*c* 2·0) (Found: C, 44·65; H, 4·15; N, 15·5%).

*5-Cyano-*1-2-*deoxy-*D-*glucopyranosyluracil.*—To a solution of 2-amino-2-deoxy-D-glucose hydrochloride (1 g.) in water (5 ml.) and 2N-sodium hydroxide (2·34 ml.) was added a solution of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (0·98 g.) in ethanol (10 ml.). The solution was warmed on a water-bath for 15 min., cooled, and treated with a solution of basic lead acetate, a solid precipitate being obtained. The lead salt was washed with water and ethanol and decomposed as a suspension in ethanol with hydrogen sulphide. Lead sulphide was removed and the filtrate evaporated to a small volume and cooled. The *pyrimidine monohydrate* (0·3 g.) crystallised from ethanol as plates, m. p. 218°, $[\alpha]_D^{20}$ +67·6° (*c* 2·07) (Found: C, 42·0; H, 4·65; N, 12·65. $C_{11}H_{13}O_7N_3.H_2O$ requires C, 41·65; H, 4·75; N, 13·25%). Absorption max. at 274 (ε 13,600) and <215 mμ (ε > 10,700). In 24 hr. at 20° the substance consumed 4·05 mols. of 0·0895N-sodium metaperiodate and liberated 2·9 mols. of formic acid.

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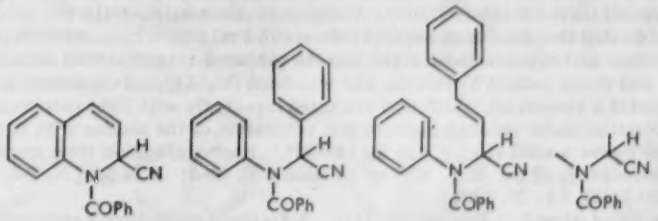
369. *Some Experiments towards the Elucidation of the Reissert Reaction.*

By R. F. Collins and T. Henshall.

During experiments on the reaction mechanism of the acid-hydrolysis of the Reissert complex,[1] 1-benzoyl-2-cyano-1 : 2-dihydroquinoline (I), the effect of anhydrous hydrochloric acid was investigated. Other workers [2,3] have shown that this reaction in various solvents gives a red oily precipitate which reacts further with water to yield benzaldehyde and quinaldamide. However, the reaction in chloroform and ethanol rapidly gives a yellow crystalline precipitate, believed to be the ethyl imidate dihydrochloride derived from 2-cyanoquinoline, together with benzaldehyde. The former product was hygroscopic and it was not possible to obtain a good analysis but it was readily converted into 2-amidinoquinoline hydrochloride by ethanolic ammonia. However, 2-cyanoquinoline under identical conditions merely gave its insoluble hydrochloride, with no further reaction.

Other workers,[4] using slightly different conditions and a longer reaction period, have claimed that 2-cyanoquinoline does form the imidic ester and ultimately the amidine. The amidine hydrochloride so obtained was described as a very hygroscopic solid for which no analysis was given. A picrate was formed which had nearly the same properties as the picrate prepared from the amidine hydrochloride in present work, and a supporting analysis was given. It appears that pure 2-amidinoquinoline hydrochloride is better prepared from the Reissert complex (I) than from 2-cyanoquinoline.

McEwen and Cobb [5] recently described the direct action of hydrochloric acid on the Reissert complex (I) in the presence of 95% ethanol and obtained ethyl quinaldate, quinaldamide, and quinaldic acid, together with benzaldehyde, but, presumably because the reagents were not anhydrous, they did not isolate any imidic ester which might have been formed initially. The conditions employed to isolate the products would almost certainly have decomposed the imidic ester to quinaldic ester or quinaldic acid.



(I) (II) (III) (IV)

We have prepared the formally analogous compounds (II) and (III) : neither yields significant quantities of benzaldehyde on acid hydrolysis. Since the completion of this work Elliott [6] has shown that *N*-benzoyl-*N*-phenylglycine nitrile yields benzoic acid on treatment with acid. From these results we infer that the complete (although partially reduced) quinoline nucleus, as in (I), is necessary, in addition to the other essential structural feature (IV), for the production of benzaldehyde.

1-Benzoyl-2-cyano-1 : 2 : 3 : 4-tetrahydroquinoline [7] contains the structure (IV), but not the 3 : 4-double bond; its acid hydrolysis yields 1 : 2 : 3 : 4-tetrahydroquinoline-2-carboxylic acid and benzoic acid but no benzaldehyde. Thus the formation of

[1] Reissert, *Ber.*, 1905, **38**, 1603.
[2] Kaufmann and Dandliker, *Ber.*, 1913, **46**, 2924.
[3] McEwen, Kindall, Hazlett, and Glazier, *J. Amer. Chem. Soc.*, 1951, **73**, 4591.
[4] Coates, Cook, Heilbron, and Lewis, *J.*, 1943, 420.
[5] McEwen and Cobb, *J. Amer. Chem. Soc.*, 1955, **77**, 5042.
[6] Elliott, *ibid.*, p. 4408.
[7] Collins, *ibid.*, p. 4921.

benzaldehyde from compound (I), in contrast to the normal acid hydrolysis of the amide and the cyano-group, must depend on the 3 : 4-double bond which would transmit any electronic disturbance at the amide group through the benzene ring to the 2-carbon atom with possible activation of the hydrogen atom at this position. It is also possible for the reverse effect to occur since we have shown that compound (I) is readily attacked at the cyano-group (more rapidly than 2-cyanoquinoline), probably forming an imidic ester salt which might effect an electronic shift *via* the 3 : 4-double bond and the benzene ring to the amide group. The presence of the 3 : 4-double bond in the compound (I) also leads to a fully aromatic ring, after the benzaldehyde is formed, and probably provides the necessary energy for the reaction to proceed.

Experimental.—*2-Amidinoquinoline hydrochloride.* 1-Benzoyl-2-cyano-1 : 2-dihydroquinoline (15·7 g.) in dry chloroform (230 mol.) and dry ethanol (4 ml.) was saturated at 0° with dry hydrogen chloride. A thick yellow precipitate was formed and after 1 week (a much shorter period can be used) at room temperature the yellow solid was collected, rapidly washed with dry ether, and placed immediately in a vacuum-desiccator. There was a strong odour of benzaldehyde during this operation. The product was analysed without further purification, owing to its hygroscopic nature, and was assumed to be crude ethyl quinoline-2-carboxyimidoate dihydrochloride (Found : C, 49·3; H, 5·75; N, 10·0; Cl, 25·9. Calc. for $C_{12}H_{12}ON_2,2HCl$: C, 52·8; H, 5·1; N, 10·25; Cl, 26·0%) containing a little excess of hydrochloric acid and water (from the atmosphere), which was not lost on drying before analysis. Approximately half of this material was treated with saturated ethanolic ammonia at 55—60° for 5 hr. The yellow product (6·7 g.) was soluble in ethanol and was precipitated therefrom by ether. Repetition of this process freed the amidine hydrochloride from ammonium chloride. The crude product was then recrystallised from ethanol and acetone, to yield pure *2-amidinoquinoline hydrochloride* (1·5 g.), m. p. 238° (Found : C, 58·0; H, 4·85; N, 20·3. $C_{10}H_9N_3,HCl$ requires C, 57·8; H, 4·8; N, 20·2%). The picrate, m. p. 263—264° (Found : N, 21·2. Calc. for $C_{16}H_{12}O_7N_6$: N, 21·0%) (Coates *et al.*[4] give m. p. 258—259° (decomp.)), was formed from the hydrochloride and was recrystallised from acetone.

The original chloroform filtrate, from the imidic ester, was concentrated and the residue steam-distilled. Extraction of the distillate with ether afforded benzaldehyde (5 g.).

α-Benzanilidophenylacetonitrile (II). α-Anilinophenylacetonitrile[5] (10 g.) in dry pyridine (30 ml.) was treated dropwise with benzoyl chloride (6·8 ml.) at <25°. Next day the mixture was poured on ice and extracted with ether, and the extract was washed with dilute hydrochloric acid, water, and dilute sodium hydroxide, and was dried ($MgSO_4$). Evaporation under reduced pressure afforded a viscous oil, which was extracted repeatedly with light petroleum (b. p. 60—80°). Evaporation under reduced pressure and trituration of the residue with light petroleum (b. p. 40—60°) gave a solid (10·7 g.), m. p. 78—81°. Recrystallisation from methanol yielded the pure *amido-nitrile* (9 g.), m. p. 87—88° (Found : C, 80·5; H, 4·95; N, 9·0. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·1; N, 9·0%).

2-Benzanilido-4-phenylbut-3-enonitrile (III). 2-Anilino-4-phenylbut-3-enonitrile[6] (10 g.) in pyridine (30 ml.) was treated dropwise with benzoyl chloride (6·5 ml.) at <25° and worked up as above. The ethereal solution of the product was concentrated *in vacuo* and afforded a red viscous oil. Approx. 2 g. of this oil were chromatographed over alumina in benzene, with ether, followed by ether–ethanol for elution. After several months crystals appeared in one of the residues obtained by evaporation of aliquot parts of the eluate. After the addition of some ether, the crystals (0·3 g.; m. p. 94—98°) were collected and recrystallised from methanol to yield *2-benzanilido-4-phenylbut-3-enonitrile* (0·2 g.), m. p. 97—98° (Found : C, 81·8; H, 5·5; N, 8·2. $C_{23}H_{18}ON_2$ requires C, 81·6; H, 5·3; N, 8·3%).

The bulk of the original solution was then treated with methanol, seeded, and kept at 0° overnight. The crystalline product was collected and recrystallised from methanol to yield the pure product (2·3 g.), m. p. 96—97°.

The filtrate from the separation of the crude product was stored for several days and a crystalline solid slowly appeared. It was collected and recrystallised from methanol and yielded a second *product* (3·1 g.), m. p. 115—117° (Found : C, 81·8; H, 5·6; N, 8·25%). The m. p. was depressed to 86—90° on admixture with the first product and to 98—105° on admixture with the anilinonitrile (m. p. 127—128°). The products are thus probably *cis–trans*-isomers.

[5] Tiemann and Piest, *Ber.*, 1882, **15**, 2029.
[6] Von Miller, Plöchl, and Jungmann, *Ber.*, 1892, **25**, 2052.

Hydrolysis of the nitrile (II). The nitrile (1 g.) was refluxed for 1·5 hr. with concentrated hydrochloric acid (10 ml.) and water (10 ml.). Steam-distillation and extraction of the basified distillate with ether gave a negligible quantity of benzaldehyde (2 : 4-dinitrophenylhydrazone, m. p. 237—238°). The alkaline aqueous steam-distillate was acidified but no benzoic acid was isolated, presumably because of the volume of water present. The residue in the flask, after the steam-distillation, was filtered off, dissolved in dilute sodium hydroxide, filtered, and acidified with acetic acid, and the product (0·45 g.), m. p. 157—158°, was collected. It recrystallised from aqueous ethanol and then from benzene, giving α-anilinophenylacetic acid (0·35 g.), m. p. 172—173° (Found : C, 74·6; H, 6·1; N, 6·25. Calc. for $C_{14}H_{13}O_2N$: C, 74·0; H, 5·7; N, 6·2%). McKenzie and Bate [10] give m. p. 174—175°. The original acid filtrate from the latter product gave a positive diazo-reaction, indicating the presence of a trace of primary aromatic amine.

Hydrolysis of the nitrile (III). The nitrile (0·5 g.) was refluxed with concentrated hydrochloric acid (5 ml.) and water (5 ml.) for 1·5 hr. Benzaldehyde could not be detected either by its odour or by treatment of the hydrolysate with 2 : 4-dinitrophenylhydrazine. Each isomer gave the same result.

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Jewry Street, Aldgate, London, E.C.3. [*Received, October 21st*, 1955.]

[10] McKenzie and Bate, *J.*, 1915, **107**, 1682.

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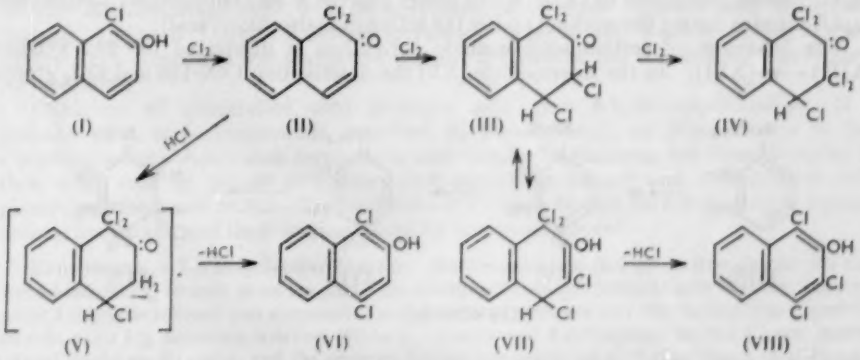
370. *Secondary Mechanisms in the Halogenation of Phenols and Aromatic Sulphonamides.*

By P. W. Robertson.

None of the mechanisms proposed hitherto accounts satisfactorily for all the complex products of halogenation of phenols or aromatic sulphonamides,[1] and the present note suggests an alternative. These reactions involve nucleophilic halogen addition (the kinetics of which have recently been investigated [2]) as well as addition and subsequent elimination of hydrogen halide.

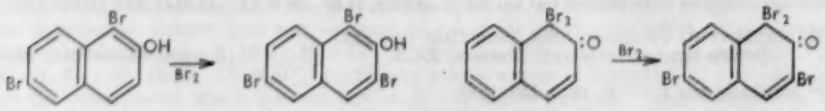


Chlorination of β-naphthol yields the products [3] shown in the annexed scheme. Electrophilic substitution gives first 1-chloro-2-naphthol (I), which by addition of chlorine

[1] Bell and Mulholland, *J.*, 1949, 2020; Bell, *J.*, 1953, 3035; 1955, 2376; Bell and Gibson, *J.*, 1954, 4635; 1955, 24.
[2] de la Mare and Robertson, *J.*, 1945, 888; Rothbaum, Ting, and Robertson, *J.*, 1948, 980.
[3] Zincke, *Ber.*, 1888, **21**, 3378; James and Woodcock, *J.*, 1951, 1931.

and elimination of hydrogen halide yields the dichloro-compound (II). This αβ-unsaturated ketone undergoes acid-catalysed nucleophilic addition of chlorine, the reactive agent being HCl_2 and the product the tetrachloro-oxotetralin (III). Further chlorination then gives the pentachloro-ketone (IV) or, if no more than 3 mols. of chlorine are used, the tetrachloro-ketone changes, *via* the enol (VII), into the trichlorophenol (VIII). 1 : 4-Dichloro-2-naphthol (VI) is produced in practice by bubbling chlorine into the reaction mixture, two mols. of chlorine being consumed: it cannot be formed by electrophilic substitution which, as shown, for example, by nitration, would yield a 1 : 6-disubstituted product; its formation is prevented by addition of sodium acetate to the acetic acid solvent, in which it acts as a base, so it follows that hydrogen chloride is required and reaction *via* the intermediate (V) (which is not isolated) can be assumed. The dichloronaphthol is however not obtained when an excess of chlorine is used, for addition of chlorine, to give the product (III), is more rapid than that of hydrogen halide.

Bromination of β-naphthol [4] takes a different course. The 1 : 6-dibromo-compound (IX), the normal disubstitution product, when further brominated in acetic acid, yields the

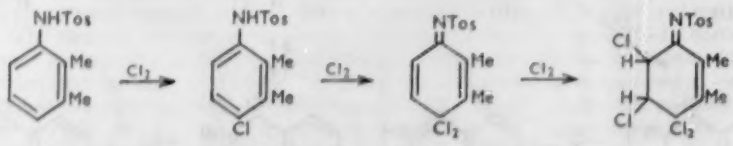


(IX) (X) (XI) (XII)

tribromonaphthol (X), probably by acid-catalysed addition of bromine to the keto-form with subsequent elimination of hydrogen bromide: in this case there is no 4-substitution because the equilibrium $-CX_2{\cdot}CO^- + HX \rightleftharpoons -CHX{\cdot}CO^- + X_2$ lies more to the right when X = Br than when X = Cl. However, in presence of sodium acetate dibromination leads to the ketone (XI), which by nucleophilic addition (involving Br_2^- ions, which may react rapidly even in the absence of H^+) followed by elimination of hydrogen halide (favoured by sodium acetate) affords the tetrabromo-ketone (XII).

In the analogous bromination of arenesulphonyl-2-naphthylamides in pyridine, Bell [1] obtained the 1 : 3-dibromo-derivative as end-product. Here, " positive " bromine cannot be the reagent, for this would merely react at the 1 : 6-positions. Reaction with Br_2^- ions probably proceeds by way of the *N*-arenesulphonyl-1 : 1 : 3-tribromo-1 : 2-dihydro-2-naphthylimine [analogous to (XII)] which passes into the *N*-arenesulphonyl-1 : 3-dibromonaphthylamine during the working up (by the action of hydrochloric acid).

The behaviour of certain sulphonamide derivatives is illustrated for 2 : 3-xylidine (XIII) ⟶ (XVI). In the intermediate (XV) the deactivating C=N·Tos and CCl_2 groups



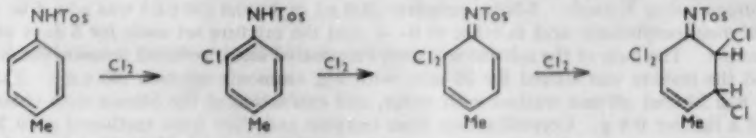
(XIII) (XIV) (XV) (XVI)

(Tos = $ArSO_2$)

should cause the electrophilic addition of chlorine to be very slow. The alternative, nucleophilic addition of chlorine may be expected to be fast, and should therefore, be the mechanism that is in operation. The isolation of the addition product (XVI) confirms this view, since methyl groups are known to reduce the rate of nucleophilic addition (*e.g.*, acrylic acid > α-methylacrylic acid, benzoquinone > 2 : 6-dimethylbenzoquinone).[2]

[4] Franzen, *J. prakt. Chem.*, 1922, **103**, 352; Fries, *Annalen*, 1930, **484**, 245.

Chlorination of a *p*-toluidine derivative (XVII) occurs by the steps (XVII—XX). In the last step, acid-catalysed 1 : 2-nucleophilic addition (by means of HCl_2) should be fast,



(XVII) (XVIII) (XIX) (XX)

and 1 : 2-electrophilic addition should be slow [as for the acid, $CHPh{:}CH{\cdot}CH{:}C(CO_2H)_2$].[5] Here again the nature of the product indicates that a nucleophilic addition process is a secondary mechanism in the halogenation.

32, Dorset Square, London, N.W.1. [*Received, November 8th*, 1955.]

[5] Evans, Watson, and Robertson, *J.*, 1950, 1624.

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371. *Heterocyclic N-Oxides. Oxides of Some Diphenylpyrazine Derivatives and of 3-Nitro- and 7-Nitro-quinoline.*

By Justus K. Landquist.

During an investigation of the chemotherapeutic properties of quinoxaline di-*N*-oxides a search was made for other heterocyclic *N*-oxides with similar antibacterial or antiprotozoal activity. Some of the closely related pyrazine *N*-oxides have already been described.[1] Certain nitroquinoline *N*-oxides bear a formal resemblance to quinoxaline 1 : 4-dioxide, and the *N*-oxides of 4-, 5-, 6-, and 8-nitroquinoline have been described.[2] 3-Nitro- and 7-nitro-quinoline *N*-oxides were made by oxidation of the corresponding nitroquinolines with monoperphthalic acid.

2 : 3-Diphenylpyrazine on oxidation with peracetic acid gave mono- and di-*N*-oxides, but 2 : 6-diphenylpyrazine gave only a monoxide, probably 2 : 6-diphenylpyrazine 4-oxide. 5 : 6-Dihydro-2 : 3-diphenylpyrazine was treated with peracetic acid in the expectation that dehydrogenation and *N*-oxidation would occur, but the product appeared to be a di-*N*-oxide of the dihydro-compound. 2 : 3-Diphenylpyrazine 1-oxide reacted with phosphoryl chloride, giving 5-chloro-2 : 3-diphenylpyrazine. Like 2- and 3-chloro-5 : 6-benzoquinoxaline [3] this compound was unreactive towards arylamines, but the chlorine was replaced by piperidine.

Oxidation of quinazoline with peracetic acid gave 4-hydroxyquinazoline. It is probable that some compounds described in the literature as *N*-oxides are in fact *C*-hydroxy-compounds; such compounds may usually be distinguished from *N*-oxides by their high melting points (2-hydroxy-5 : 6-diphenylpyrazine [4] and 2-hydroxy-3 : 5-diphenylpyrazine [5] melt at 243—244° and 270—272°, respectively), their solubility in aqueous sodium hydroxide, and their sparing solubility in organic solvents.

Experimental.—*3-Nitroquinoline N-oxide.* 3-Nitroquinoline (8·7 g.) in dry dioxan (60 c.c.) was added during 10 min. to an ice-cold 0·5N-solution of monoperphthalic acid in ether (125 c.c.). After 3 days the solvent was evaporated under reduced pressure and the residue was stirred for 30 min. with 5% ammonia solution (90 c.c.). Unchanged 3-nitroquinoline (4·5 g.) was filtered off and washed with water, and the aqueous filtrate was extracted with chloroform (3 × 80 c.c.). Evaporation of the dried (Na_2SO_4) extract and repeated crystallisation of the residue (1·2 g.)

[1] Newbold and Spring, *J.*, 1947, 1183.
[2] Ochiai, Ishikawa, and Zai-Ren, *J. Pharm. Soc. Japan*, 1943, **63**, 280; Gouley, Moersch, and Mosher, *J. Amer. Chem. Soc.*, 1947, **69**, 303; Bachman and Cooper, *J. Org. Chem.*, 1944, **9**, 302.
[3] Landquist, *J.*, 1953, 2816.
[4] Karmas and Spoerri, *J. Amer. Chem. Soc.*, 1952, **74**, 1580.
[5] Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny, *J.*, 1949, 2707.

from ethanol yielded **3-*nitroquinoline* N-*oxide*** (0·5 g.) as yellow crystals, m. p. 192—193° (Found : C, 56·8; H, 3·3; N, 14·4. $C_9H_6O_3N_2$ requires C, 56·8; H, 3·15; N, 14·7%). The same *N*-oxide was obtained by oxidation with 1·2M-peracetic acid at 50° overnight.

7-Nitroquinoline* N-*oxide*.** 7-Nitroquinoline (5·0 g.) in dioxan (50 c.c.) was added to a 25% excess of monoperphthalic acid in ether at 0—5° and the mixture set aside for 5 days at room temperature. The bulk of the solvent was then evaporated under reduced pressure (bath temp. 50°) and the residue was stirred for 30 min. with 5% ammonia solution (60 c.c.). The solid (4·5 g.) was filtered off and washed with water, and extraction of the filtrate with chloroform afforded a further 0·8 g. Crystallisation from benzene and then from methanol gave ***7-nitroquinoline* N-*oxide (1·6 g.), yellow crystals, m. p. 174—175° (Found : C, 57·2; H, 3·5; N, 14·6%).

Oxidation of **2 : 3-*Diphenylpyrazine*.** **2 : 3**-Diphenylpyrazine (5·8 g.) and 1·2M = peracetic acid (80 c.c.) were heated overnight at 50°, cooled, and diluted with water to 350 c.c.; **2 : 3-*diphenylpyrazine* 1-*oxide*** (2·9 g.) was removed by filtration and washed with water. It crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 171—172° (Found : C, 76·6; H, 4·8; N, 10·95. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%). The aqueous filtrate was cooled in ice and made just alkaline (Brilliant yellow) with sodium hydroxide, and the precipitated **2 : 3-*diphenylpyrazine* 1 : 4-*dioxide*** (2·0 g.) was collected and washed with water. Extraction of the mother liquors with chloroform afforded 1 g. of impure material. The product crystallised from ethanol in platelets, m. p. 262° (decomp.) (Found : C, 72·4; H, 4·55; N, 10·7. $C_{16}H_{12}O_2N_2$ requires C, 72·6; H, 4·55; N, 10·6%).

By using similar oxidation conditions the following were prepared : **5 : 6-*dihydro*-2 : 3-*diphenylpyrazine* 1 : 4-*dioxide***, needles, m. p. 244°, from 2-ethoxyethanol (Found : C, 71·9; H, 6·2; N, 11·0. $C_{16}H_{14}O_2N_2$ requires C, 72·1; H, 5·25; N, 10·5%), and **2 : 6-*diphenylpyrazine* 4(?)-*oxide***, needles, m. p. 200—201°, from ethanol (Found : C, 77·3; H, 4·85; N, 11·4. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

***2-Chloro*-5 : 6-*diphenylpyrazine*.** **2 : 3**-Diphenylpyrazine 1-oxide (1·6 g.) and phosphoryl chloride (6 c.c.) were boiled under reflux for 20 min. and then poured on ice (100 g.), and the mixture was made alkaline with potassium hydroxide. The precipitated oil solidified slowly and the crude solid (1·7 g.; m. p. 123—124°) was washed with water, dried, and crystallised from ethanol. 2-Chloro-5 : 6-diphenylpyrazine was obtained as prisms, m. p. 125—126°, from *cyclo*hexane (Found : C, 72·2; H, 4·2; N, 10·6. Calc. for $C_{16}H_{11}N_2Cl$: C, 72·0; H, 4·1; N, 10·5%). Karmas and Spoerri [4] found m. p. 126—127°.

5 : 6-*Diphenyl*-2-*piperidino*-*pyrazine*. 2-Chloro-5 : 6-diphenylpyrazine (2·6 g.) and piperidine (9 c.c.) were boiled under reflux for 1·5 hr. and poured into water. The precipitate hardened when rubbed, and was crystallised from ethanol, giving **5 : 6-*diphenyl*-2-*piperidinopyrazine*** (2·4 g.) m. p. 127—129° (Found : C, 79·9; H, 6·5; N, 13·3. $C_{21}H_{21}N_3$ requires C, 80·0; H, 6·7; N, 13·3%).

IMPERIAL CHEMICAL (PHARMACEUTICALS) LIMITED,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9.

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372. *A Simple Approximation to the Resonance Energies of Aromatic Molecules.*

By A. L. GREEN.

ALTHOUGH many approximate formulæ, both empirical [1] and based on perturbation treatments of more rigorous quantum-mechanical methods,[2] have been given for the calculation of resonance energies, the simple dependence of the resonance energies of aromatic molecules containing only six-membered rings on the number of bonds in the molecule, *i.e.*, $E_{res.} = kn$, has not been reported. If $k = \beta/3$, then the energy is given in terms of the molecular-orbital resonance integral β. The slightly greater resonance energies of angular molecules compared with those of their linear isomers can be corrected by addition of $m\beta/10$, where

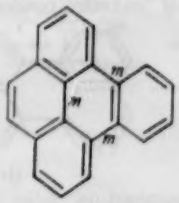
[1] (*a*) Brown, *Trans. Faraday Soc.*, 1950, **46**, 1013; (*b*) Carter, *ibid.*, 1949, **45**, 597; (*c*) Wheland, "The Theory of Resonance," John Wiley and Sons, New York, 1944, p. 79.

[2] (*a*) Wheland, *J. Chem. Phys.*, 1935, **3**, 230; (*b*) Daudel and Vroelant, *Bull. Soc. chim. France*, 1949, **16**, 217; (*c*) Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3345; (*d*) Dewar and Petitt, *J.*, 1954, 1617.

m is the number of bonds contained in one benzene ring in the molecule and linking two others, giving the complete formula :

$$E_{res.} = (n/3 + m/10)\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The calculation is illustrated below for **4** : 5-benzopyrene :



$n = 24$, $m = 3$, $E_{res.} = 8{\cdot}30\beta$.

In Table 1 the resonance energies calculated for a number of aromatic molecules are compared with those obtained by the complete molecular-orbital method by Wheland's method,[1c,2a] in which the resonance energy is directly proportional to the number of single bonds in any "Kekulé" representation of the aromatic system, and by Daudel and Vroelant's method [2b] in which the total π-electron energy is an additive function of the number of bonds. Wheland's method does not allow for the variation in resonance energy of isomers and could be improved by some factor such as our "m" term.

TABLE 1. *Resonance energies (in units of β) calculated by various approximate formulæ compared with accurate molecular-orbital values.*

Compound *	Accurate †	This note	Wheland ‡	Daudel and Vroelant ‡
Benzene	2·00 [a]	2·00	1·82	1·80
Naphthalene	3·68 [a]	3·67	3·64	3·52
Anthracene	5·31 [a]	5·33	5·46	5·24
Phenanthrene	5·45 [a]	5·43	5·46	5·33
Pyrene	6·51 [b]	6·43	6·67	6·54
Naphthacene	6·93 [b]	7·00	7·27	6·94
Benzanthracene	7·10 [b]	7·10	7·27	7·05
Chrysene	7·19 [b]	7·20	7·27	7·14
Triphenylene	7·27 [b]	7·30	7·27	7·21
Perylene	8·25 [c]	8·20	8·50	8·40
4 : 5-Benzopyrene	8·34 [d]	8·30	8·50	8·40
Pentacene	8·54 [e]	8·67	9·10	8·65
Pentaphene	8·76 [e]	8·77	9·10	8·78
1 : 2-5 : 6-Dibenzanthracene	8·88 [e]	8·87	9·10	8·85
Picene	8·94 [e]	8·97	9·10	8·95
2 : 3-6 : 7-Dibenzopyrene	9·95 [d]	9·97	10·31	10·07
2 : 3-4 : 5-Dibenzopyrene	10·03 [d]	10·07	10·31	10·22
Hexacene	10·16 [e]	10·33	10·92	10·41
2 : 3-8 : 9-Dibenzochrysene	10·48 [d]	10·53	10·92	10·59
Coronene	10·57 [e]	10·60	10·92	10·84
Tetrabenzonaphthalene	10·80 [f]	10·93	10·92	10·90
Tetrabenzanthracene	12·55 [f]	12·60	12·73	12·61
Chalcacene	12·84 [g]	12·83	13·34	13·32

* The numbering is that of the "Ring Index."

† Accurate values are taken from : (*a*) Brown, *Trans. Faraday Soc.*, 1950, **46**, 1013; (*b*) Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906; (*c*) Baldock, Berthier, and Pullman, *ibid.*, 1949, **228**, 931; (*d*) Chalvet and Peltier, *ibid.*, 1955, **240**, 1709; (*e*) Moffitt and Coulson, *Proc. Phys. Soc.*, 1948, **60**, *A*, 309; (*f*) Herraez Zarza, *Anales Fis. Quim.*, 1955, **51**, *B*, 305; (*g*) Coulson, Bradburn, and Rushbrooke, *Proc. Roy. Soc. Edinburgh*, 1946, **62**, *A*, 336.

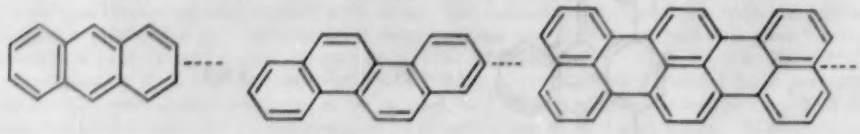
‡ These approximations are derived from valence-bond theory and give results in terms of the valence-bond exchange integral, α. These have been multiplied by 1·82 to give comparable resonance energies in terms of the molecular-orbital resonance integral, β.

Coulson and his co-workers [3,4] have studied large condensed aromatic systems. Their numerical results indicate that the resonance energies depend simply on the number of

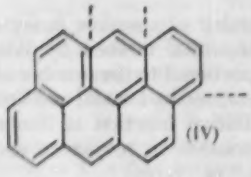
[3] Coulson, Bradburn, and Rushbrooke, *Proc. Roy. Soc. Edinburgh*, 1946, **62**, *A*, 336.
[4] Coulson and Rushbrooke, *ibid.*, p. 350.

bonds but vary with the shape of the molecule. In our formula this variation is corrected by m. Coulson and Rushbrooke [4] give the resonance energies per atom of several infinitely large structures; for these structures they can be easily calculated by the present formula and some results are given in Table 2.

TABLE 2. *Resonance energies (in units of β) per atom of "infinite" condensed aromatic systems.*



(I) (II) (III)



(IV)

Structure	Accurate	Approximate
"Polyacene" (I)	0·403	0·417
"Skewed linear" (II) ...	0·437	0·442
"Polynaphthylene" (III)	0·461	0·463
"Graphite" (IV)	0·576	0·550

The formula is also related to the "annelation" energy formula used by Brown,[1a] who found that, for any aromatic molecule that can be constructed by the fusion of two simpler molecules, the resonance energy is given approximately by :

$$E_{res.} = E_{res.}^{(1)} + E_{res.}^{(2)} + [2{\cdot}15(p_a p_b)^{\frac{1}{2}} - 1{\cdot}73]\beta$$

where $E_{res.}^{(1)}$ and $E_{res.}^{(2)}$ are the separate resonance energies and p_a and p_b are the mobile bond orders of the bonds being fused. If in every case $E_{res.}^{(2)}$ is that of benzene, then

$$E_{res.} = E_{res.}^{(1)} + [0{\cdot}27 + 2{\cdot}15(0{\cdot}67p_b)^{\frac{1}{2}}]\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Aromatic bonds at which fusion can occur are generally of three types, similar to the 2 : 3-, 1 : 2-, and 9 : 10-bonds in phenanthrene with mobile bond orders about 0·61, 0·72, and 0·78, respectively. If these values are substituted in equation (2) the additional resonance energies due to the annelation of a single benzene ring at these three types of bond are : 2 : 3-, 1·64β; 1 :2-, 1·76β; 9 : 10-, 1·83β. Annelation of a benzene ring requires the addition of five bonds to the molecule. If fusion occurs at a 1 : 2-bond one "m" type bond is created, while if at a 9 : 10-bond, there are two. Thus the additional resonance energies are 1·67β, 1·77β, and 1·87β, so that the two formulæ are almost equivalent. However, Brown's formula is not applicable to condensed structures such as pyrene, perylene, or coronene for which the simple formula still gives good agreement.

CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT,
PORTON, WILTS.

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373. *Oxanil.*

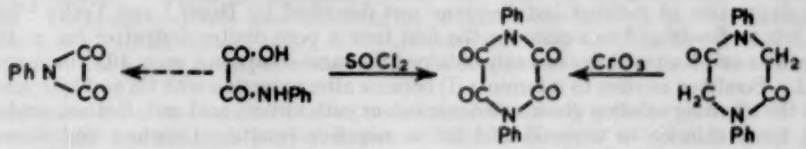
By D. BUCKLEY and H. B. HENBEST.

WARREN and BRIGGS [1] reported that treatment of oxanilic acid (I) with thionyl chloride gave a high-melting compound which they regarded as oxanil (II) on the basis of analytical data and a molecular-weight determination in boiling nitrobenzene. The yield was not stated.

In view of the unique ring structure of the formulation (II), this reaction has been reinvestigated. When a solution of oxanilic acid in purified thionyl chloride was heated

[1] Warren and Briggs, *Ber.*, 1931, **64**, 26.

under reflux for 12 hours and the precipitate crystallised from nitromethane, a 12% yield of a crystalline compound, subliming at 335—340°, was obtained (Warren and Briggs state that their compound had not melted at 320°). The analytical data for this compound



agreed with $C_8H_5O_2N$, and the compound gave aniline on hydrolysis with aqueous alkali and a single band at 1709 cm.$^{-1}$ in the carbonyl region of the infrared spectrum.

The suspicion that this "oxanil" might be the long-known 2 : 3 : 5 : 6-tetraoxo-1 : 4-diphenylpiperazine (III) was confirmed by comparison with authentic material prepared [2] by chromic acid oxidation of the 2 : 5-dioxo-compound (IV). Both (III) and (IV) were converted in high yield into 1 : 4-diphenylpiperazine by reduction with lithium aluminium hydride in boiling dioxan.

The similarity of the method of preparation and of the properties of the high-melting products prepared from oxanilic acid by Warren and Briggs and by the present authors make it reasonably certain that the earlier workers also obtained (III), and that oxanil (II) has yet to be prepared.

Experimental.—(M. p.s were determined on a Kofler block.)

Action of thionyl chloride on oxanilic acid. A mixture of the acid (5 g.; prepared by Tingle and Bates's method [3]) and thionyl chloride (25 c.c.; purified by distillation from quinoline and from linseed oil) was heated under reflux for 15 hr. The cooled suspension was filtered and the solid product crystallised from nitromethane, to give 2 : 3 : 5 : 6-tetraoxo-1 : 4-diphenylpiperazine (0·48 g.), subliming at 335—340° (Found : C, 65·25; H, 3·45; N, 9·65. Calc. for $C_{16}H_{10}O_4N_2$: C, 65·3; H, 3·45; N, 9·5%).

The compound synthesised by Abenius's method [2] also sublimed at 335—340°. Both products gave identical infrared spectra in Nujol suspensions; carbonyl peak at 1709 cm.$^{-1}$. Both products showed $\lambda_{max.}$ 2250 Å and $\lambda_{min.}$ 2160 Å in the ultraviolet region (in saturated dioxan solutions).

1 : 4-*Diphenylpiperazine.* The tetraoxo-compound (0·26 g.) was extracted in a Soxhlet thimble above a solution of lithium aluminium hydride (0·16 g.) in boiling dioxan (100 c.c.). After 4 hr. the compound had dissolved, and the product was isolated with ether. The crude product in benzene solution was filtered through alumina (10 g.) yielding material (0·17 g.), m. p. 166—168°, raised to 169—170° by crystallisation from ether–light petroleum (Found : C, 80·4; H, 7·35; N, 11·65. Calc. for $C_{16}H_{18}N_2$: C, 80·65; H, 7·6; N, 11·75%). Identical results were obtained by reduction of the tetraoxo-compound from either route. Wedekind and Bruch [4] record m. p. 164—165° for this compound.

THE UNIVERSITY, MANCHESTER 13. [*Received, December 9th*, 1955.]

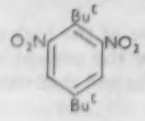
[2] Hausdorfer, *Ber.*, 1889, **22**, 1797; Abenius, *J. prakt. Chem.*, 1908, **41**, 80.
[3] Tingle and Bates, *J. Amer. Chem. Soc.*, 1909, **31**, 1237.
[4] Wedekind and Bruch, *Annalen*, 1929, **471**, 88.

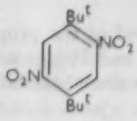
374. *The Dinitration of* p-*Di-*tert.*-butylbenzene.*

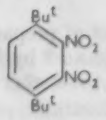
By F. Bell and K. R. Buck.

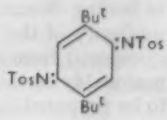
The dinitration of *p*-di-*tert.*-butylbenzene was described by Bauer [1] and Verley [2] but it was left to Boedtker [3] to isolate for the first time a pure dinitro-derivative (m. p. 191°). Carpenter and Easter [4] have recently obtained the same compound, m. p. 193°, in improved yield. Boedtker ascribes to it formula (I) because after reduction with tin and hydrochloric acid the resulting solution gives an intense colour with nitrous acid and, further, oxidation with ferric chloride or chromic acid led to negative results. Crawford and Stewart [5] have emphasized the difficulty which must attend the preparation of a compound in which the *tert.*-butyl group is flanked by two nitro-groups but since the experiments of Carpenter, Easter, and Wood [4,6,7] had provided at least twelve examples of this type of structure there had been little reason to question the correctness of Boedtker's conclusion, lightly founded though it appeared.

On repeating this dinitration we found that the product, which was very complex, contained Boedtker's compound together with an isomer, m. p. 141°. The dipole moment of the compound of m. p. 191° in benzene solution was indistinguishable from zero; that of


(I)


(II)


(III)


(IV)

the compound of m. p. 141° was 2·3 D. It thus appears that Boedtker's compound must be the 2 : 5-dinitro-compound (II) and it may be recalled that Kofod, Kumar, and Sutton [8] found a negligible moment for the dibromo-compound to which they ascribed the analogous constitution. The isomer, for which (I) and (III) are possible formulæ, is regarded as (I) by comparison with the dinitrobenzenes for which the dipole moments are: *ortho* 5·98; *meta* 3·78 D; *para*, zero.[9] Further, structure (III) was rejected on chemical grounds because the compound, m. p. 141°, could be recovered unchanged from boiling piperidine, which Le Fèvre and Turner [10] found to react readily with *o*-dinitro-compounds, and, also, the product of reduction of the compound did not condense with phenanthraquinone as an *o*-diamine would be expected to do. The low dipole moment compared with that of *m*-dinitrobenzene suggests that the nitro-groups are laterally displaced about 12° away from the *tert.*-butyl group or, alternatively, that they have moved out of the plane of the benzene ring, or have suffered both types of displacement.

Additional evidence in favour of structure (II) for Boedtker's compound was obtained by preparing from it a *p*-quinonoid compound, such as he sought but failed to obtain. The dinitro-compound was reduced to the diamine from which was prepared the ditoluene-*p*-sulphonyl derivative. This on oxidation with *N*-bromosuccinimide in pyridine gave an almost quantitative yield of the corresponding ditoluene-*p*-sulphonimido-derivative (IV; Tos = *p*-$C_6H_4Me{\cdot}SO_2$).

1 : 4-Di-*tert.*-butyl-2 : 5-ditoluene-*p*-sulphonamidobenzene, on crystallisation from *o*-dichlorobenzene (nominal), separated with 1 mol. of *p*-dichlorobenzene, which was tenaciously

[1] Bauer, *Ber.*, 1896, **27**, 1608.
[2] Verley, *Bull. Soc. chim. France*, 1898, **19**, 72.
[3] Boedtker, *ibid.*, 1906, **35**, 835.
[4] Carpenter and Easter, *J. Org. Chem.*, 1954, **19**, 77.
[5] Crawford and Stewart, *Nature*, 1952, **176**, 322.
[6] Carpenter and Easter, *J. Org. Chem.*, 1951, **16**, 618; 1954, **19**, 77.
[7] Carpenter, Easter, and Wood, *ibid.*, 1951, **16**, 586.
[8] Kofod, Kumar, and Sutton, *J.*, 1951, 1790.
[9] Partington, "Advanced Treatise on Physical Chemistry," Longmans, London, 1954, Vol. V, p. 499.
[10] Le Fèvre and Turner, *J.*, 1927, 1113; see also Le Fèvre and Le Fèvre, *J.*, 1935, 964.

held. This is a remarkable example of selective action for the percentage of *p*-dichlorobenzene in *o*-dichlorobenzene (B.D.H.) is presumably quite low. Neither *p*-di-*tert.*-butylbenzene nor *p*-ditoluene-*p*-sulphonamidobenzene combined with *p*-dichlorobenzene.

Experimental.—Physical measurements. These were made on dilute solutions in benzene at 20°. Dielectric constants were measured by a heterodyne beat method, and refractive indices with a Pulfrich refractometer. The customary correction (of doubtful validity) of 5% of P_E for P_A was ignored as this would affect only the second decimal place in a moment as high as 2·3 D.

Preparations. *p*-Di-*tert.*-butylbenzene (20 g.) was mononitrated by the method of Carpenter, Easter, and Wood,[7] the crude product further nitrated by Boedtker's method, and the final product recrystallised from acetic acid. The first crops consisted of 1 : 4-di-*tert.*-butyl-2 : 5-dinitrobenzene, m. p. 191° (6 g.). From the later crops there was isolated 1 : 4-*di*-tert.-*butyl*-2 : 6-*dinitrobenzene*, which formed stout needles, m. p. 141° (1 g.) (Found : C, 60·1; H, 6·9. $C_{14}H_{20}O_4N_2$ requires C, 60·0; H, 7·1%). The final mother-liquors yielded pale yellow needles (1·6 g.), m. p. 74—90°, which were not examined further. The result was slightly less favourable when *p*-di-*tert.*-butylbenzene was dinitrated directly by Boedtker's method.

Reduction of 1 : 4-di-*tert.*-butyl-2 : 5-dinitrobenzene by iron powder in boiling ethanol with a little hydrochloric acid for 24 hr. gave a very dark diamine, which could not be obtained pure. With toluene-*p*-sulphonyl chloride in pyridine it gave a *ditoluene*-p-*sulphonyl derivative*, which readily crystallised from commercial *o*-dichlorobenzene in "solvated" needles, m. p. 272° (decomp.) (Found : C, 60·2; H, 5·9. $C_{28}H_{36}O_4N_2S_2,C_6H_4Cl_2$ requires C, 60·4; H, 5·9%). Above 170° the crystals became opaque and pure *p*-dichlorobenzene, m. p. and mixed m. p. 53°, was evolved (Found, after this treatment : C, 63·8; H, 6·7. $C_{28}H_{36}O_4N_2S_2$ requires C, 63·7; H, 6·8%). On addition of *N*-bromosuccinimide to an equal weight of this compound, dissolved in pyridine, a yellow precipitate began to separate. Precipitation was completed by addition of dilute hydrochloric acid, and the product recrystallised from *o*-dichlorobenzene to yield 1 : 4-*di*-tert.-*butyl*-2 : 5-*ditoluene*-p-*sulphonimidobenzene* (IV) in bright yellow prisms, m. p. 258—260° (decomp.) (Found : C, 63·6; H, 6·5. $C_{28}H_{34}O_4N_2S_2$ requires C, 63·9; H, 6·5%).

The authors are indebted to Dr. J. W. Minnis for the microanalyses and to the Carnegie Trust for the Universities of Scotland for a grant.

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375. *Phenoxyacetic Acid.*

By R. BRETTLE.

THE condensation of phenol and chloroacetic acid in aqueous alkali [1-3] gave poor yields of phenoxyacetic acid. This acid was, however, obtained in excellent yield from the hydrolysis of ethyl phenoxyacetate, which was prepared by the reaction of phenol with ethyl chloroacetate and sodium iodide in acetone, in the presence of potassium carbonate (cf. ref. 4).

The preparation of phenoxyacetone from phenoxyacetic acid by Blaise's general method [5] is also recorded.

Experimental.—Phenoxyacetic acid. Phenol (18·5 g., 1 mol.), ethyl chloroacetate (25 g., 1 mol.), sodium iodide (30 g., 1 mol.), and anhydrous potassium carbonate (28 g.) were refluxed for 12 hr. in dry acetone (100 ml.). The mixture was then stirred into a large volume of water, and the solution extracted with ether. Unchanged phenol (4·4 g.) was removed with aqueous alkali. Distillation then gave ethyl phenoxyacetate (21·8 g., 62%), b. p. 140—144°/24 mm., which was hydrolysed by 10% aqueous potassium hydroxide, affording phenoxyacetic acid (17·0 g., 90%), m. p. 99° (Koelsch [3] records m. p. 98—99°).

Phenoxyacetone. An ice-cold solution of phenoxyacetyl chloride [from thionyl chloride

[1] Mameli, *Gazzetta*, 1926, **56**, 762.
[2] van Alphen, *Rec. Trav. chim.*, 1926, **46**, 148.
[3] Koelsch, *J. Amer. Chem. Soc.*, 1931, **53**, 304.
[4] Mauthner, *J. prakt. Chem.*, 1937, **148**, 95.
[5] Blaise and Piccard, *Ann. Chim. phys.*, 1912, **26**, 274.

and the acid (8 g.) in benzene] in toluene (15 ml.) was gradually added to a vigorously stirred solution of methylzinc iodide [from methyl iodide (21 g.) and zinc–copper couple [6] (18 g.)] in toluene (20 ml.) and ethyl acetate (5 ml.). The mixture was then poured on ice. Phenoxyacetone (2·6 g., 32·5%), b. p. 127—128°/23 mm., was isolated by the usual procedure, and purified through its bisulphite compound.[7] The semicarbazone had m. p. 172° (from ethanol) (Stoemer [8] records m. p. 173°).

DEPARTMENT OF BIOCHEMISTRY, OXFORD UNIVERSITY. [*Received, December 14th*, 1955.]

[6] Howard, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 677.
[7] Stoermer, *Ber.*, 1895, **28**, 1253.
[8] *Idem, Annalen*, 1900, **312**, 273.

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376. *The Preparation of* [^{14}C]*Dimethylamine and* [^{14}C]*Dimethylnitrosamine.*

By (MRS.) A. H. DUTTON and D. F. HEATH.

^{14}C-LABELLED dimethylamine and dimethylnitrosamine were prepared from labelled methyl iodide in high yield on a 0·1 g. scale. Excess of *N*-methyltoluene-*p*-sulphonamide was converted into its dimethyl homologue with methyl iodide in alcoholic potassium hydroxide; the dimethyl was separated from the methyl compound by extraction of the former with benzene from alkaline solution, and was hydrolysed. The dimethylamine released was separated by distillation from 2N-sodium hydroxide and estimated by titration (yield 78% on methyl iodide). The hydrochloride was concentrated to a small volume and converted nearly quantitatively into dimethylnitrosamine with sodium nitrite in glacial acetic acid. The product was separated and concentrated by distillation from 3N-sodium hydroxide, and estimated by the method of Heath and Jarvis.[1]

Trial runs presented two features of interest. First, the dimethyltoluene-*p*-sulphonamide melted at 80·6—81·1°, 6° lower than given by Steinkopf.[2] So we made the compound also from dimethylamine and toluene-*p*-sulphonyl chloride, and obtained a recrystallised product, m. p. 80·4—81·1°. Chaplin and Hunter [3] also give m. p. 80—81°, which therefore appears to be correct. Secondly, neither of the two known methods for hydrolysing sulphonamides is simple. Hinsberg [4] used concentrated hydrochloric acid at 150—160°, Fischer [5] concentrated hydriodic acid and phosphonium iodide at 100°. Dimethylamine is released quantitatively from dimethylsulphonamide by the action of concentrated hydriodic acid alone for 2 hr. at 100°. The method is relatively simple and safe, and should be applicable to the preparation of other amines.

Experimental.—*N*-Methyltoluene-*p*-sulphonamide, prepared by the method of Remsen and Palmer,[6] had m. p. 77·5—78·4°. Reverdin [7] gives m. p. 78—79°.

Labelled NN-dimethyltoluene-p-sulphonamide. Labelled methyl iodide (0·1 mc in 2·6 mg.), purchased from the Radiochemical Centre, Amersham, Bucks., was diluted with inactive methyl iodide in a vacuum manifold system. The total weight, calculated from the pressure in a bulb, was 247 mg. (1·74 mmoles). This was frozen by liquid nitrogen into a bulb containing methyltoluene-*p*-sulphonamide (370 mg., 2·0 mmoles), potassium hydroxide (130 mg., 2·28 mmoles), and 70% aqueous ethanol (4 ml.). The bulb was sealed under a vacuum and kept at 76° in a carbon tetrachloride vapour bath for 72 hr. The mixture was then transferred to a flask and concentrated. Sodium hydroxide (35 ml.; 3N) was added and the solution extracted with benzene (40 ml.). The benzene layer was washed with 3N-sodium hydroxide (15 ml.) and concentrated to dryness in a heavy-walled tube of 10 ml. capacity (yield, 270 mg., 78% on

[1] Heath and Jarvis, *Analyst*, 1955, **80**, 613.
[2] Steinkopf, *J. prakt. Chem.*, 1927, **117**, 25.
[3] Chaplin and Hunter, *J.*, 1937, 1114.
[4] Hinsberg, *Annalen*, 1891, **265**, 179.
[5] Fischer, *Ber.*, 1915, **48**, 93.
[6] Remsen and Palmer, *Amer. Chem. J.*, 1888, **8**, 241.
[7] Reverdin, *Ber.*, 1909, **42**, 1526.

methyl iodide). The purity of the labelled product was not checked. M. p.s were taken in trial runs, with the results already described.

Dimethylamine. Hydriodic acid (8 ml.; *d* 1·94) was added to the dimethylamide in the bulb, and the bulb was sealed and kept at 100° for 2 hr. in a steam-bath. The contents were then diluted and extracted with benzene to remove by-products. The benzene layer was washed with water, the aqueous layer and washings were treated with sodium hydroxide (12 g. per 100 ml. of solution), and half the solution was distilled into 0·1N-hydrochloric acid (15 ml.). The dimethylamine was estimated by titration after redistillation from sodium hydroxide solution (yield, 100% on dimethyltoluene-*p*-sulphonamide).

Dimethylnitrosamine. The dimethylamine solution was slightly acidified with hydrochloric acid and concentrated to 5 ml., and glacial acetic acid (5 ml.) and sodium nitrite (3 g.) were added and allowed to react for 10 min. at 25°. The product was diluted to 45 ml., sodium hydroxide (7 g.) added, and half the mixture distilled. The distillate contained the dimethylnitrosamine, which was estimated polarographically [1] (yield, 98·8 mg., 99% on dimethylamine, 77% on methyl iodide).

Identification and estimation of products. Dimethylnitrosamine was prepared as a dilute aqueous solution, from which it is not readily separated. The polarographic wave-form agreed with that of samples of known purity. Dimethylamine has been estimated by conversion into dimethylnitrosamine and polarographic estimation of the product.[2] In our experiments the estimation of dimethylnitrosamine constitutes an estimation of dimethylamine, and agrees within experimental error with the yield estimated by titration.

MEDICAL RESEARCH COUNCIL, TOXICOLOGY RESEARCH UNIT, SERUM RESEARCH INSTITUTE, WOODMANSTERNE ROAD, CARSHALTON, SURREY. [*Received, December 15th*, 1955.]

[2] English, *Analyt. Chem.*, 1951, **23**, 344.

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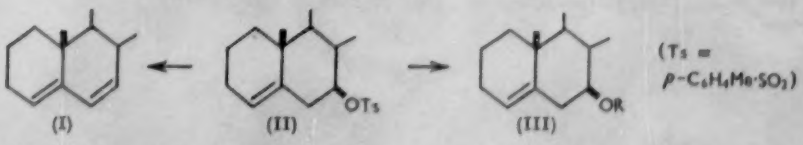
377. *Steroids and Walden Inversion. Part XXXI.*[*] *The Solvolysis of Cholest-4-en-7β-yl (ψ-Cholesteryl) Toluene-p-sulphonate.*

By C. W. SHOPPEE, G. H. R. SUMMERS, and R. J. W. WILLIAMS.

METHANOLYSIS of cholest-4-en-7β-yl (ψ-cholesteryl) toluene-*p*-sulphonate (II) in the presence or absence of potassium acetate has been shown [1] to yield cholesta-4 : 6-diene (I) and a methyl ether provisionally regarded as 7β-methoxycholest-4-ene (III; R = Me); the identity of the latter compound has now been confirmed by its demethylation to cholest-4-en-7β-ol (ψ-cholesterol) (III; R = H). Acetolysis of the ester (II) with acetic acid and potassium acetate furnished cholesta-4 : 6-diene (11%) (I) and cholest-4-en-7β-yl acetate (70%) (III; R = Ac); hydrolysis in aqueous acetone in the presence of potassium acetate yielded the diene (14·5%) (I) and the alcohol (78%) (III; R = H). Reduction of the toluenesulphonate (II) with lithium aluminium hydride gave cholest-4-ene (85%) unaccompanied by 5 : 7-*cyclo*cholestane (cf. Karrer and Schmid [2]).



(I) (II) (III)

It thus appears that reactions which convert 3β-substituted Δ^5-steroids into derivatives of 3 : 5-*cyclo*cholestane do not permit the conversion of cholest-4-en-7β-yl toluene-*p*-sulphonate into derivatives of 5 : 7-*cyclo*cholestane even though intervention of the π-electrons of the 4 : 5-double bond does occur to preserve configuration at $C_{(7)}$. The

[*] Part XXX, *J.*, 1956, 1649.

[1] Cremlyn, Rees, and Shoppee, *J.*, 1954, 3790.
[2] Karrer and Schmid, *Helv. Chim. Acta*, 1949, **32**, 1371.

predominant behaviour is replacement with retention of configuration [S_Ni] accompanied by elimination [$E1$],[3,4] insofar as weakly nucleophilic agents are involved.

Experimental.—All rotations are in $CHCl_3$.

Cholest-4-en-7β-yl toluene-*p*-sulphonate, m. p. 134—136°, $[\alpha]_D$ +19° (*c* 0·9), was refluxed with methanol and anhydrous potassium acetate (cf. Cremlyn *et al.*[1]). Chromatography of the product yielded cholesta-4 : 6-diene, m. p. 87—90°, $[\alpha]_D$ +9° (*c* 0·82), and an oily methyl ether, $[\alpha]_D$ +71° (*c*, 1·0), $\lambda_{max.}$ 211 mμ (log ε 3·41).

The methyl ether (155 mg.) in acetic acid (15 c.c.) and water (0·7 c.c.) was refluxed with hydrobromic acid (0·7 c.c.; 60%) for 1·5 hr. The dark red solution was diluted with water and extracted with ether. The ethereal extract, after being washed with saturated sodium hydrogen carbonate solution and water, yielded on evaporation a brown oil which was chromatographed on aluminium oxide (6 g.). Elution with pentane, benzene–pentane (1 : 9; 1 : 1), and benzene gave yellow oils, whilst elution with ether and ether–acetone (1 : 1) gave cholest-4-en-7β-ol (17 mg.), m. p. and mixed m. p. 118—121°, $[\alpha]_D$ +80° (*c* 0·7).

*Acetolysis of cholest-4-en-7β-yl toluene-*p*-sulphonate.* This toluene-*p*-sulphonate (500 mg.) and anhydrous potassium acetate (800 mg.) in acetic acid (24 c.c.) were heated at 95° under anhydrous conditions for 4 hr. The acetic acid was evaporated under reduced pressure and the product, a yellow oil (394 mg.), isolated in the usual way and chromatographed on neutralised aluminium oxide (Woelm; activity I; 24 g.); elution with pentane (12 × 20 c.c.) gave cholesta-4 : 6-diene (38 mg.), m. p. 88—89°, $[\alpha]_D$ +9° (*c* 0·3), whilst elution with benzene–pentane (1 : 1) (5 × 20 c.c.) and benzene (3 × 20 c.c.) gave cholest-4-en-7β-yl acetate (276 mg.), m. p. 94—96°, $[\alpha]_D$ +72° (*c* 0·92) (cf. Petersen and Chen [5]).

*Hydrolysis of the toluene-*p*-sulphonate.* The toluene-*p*-sulphonate (500 mg.) in acetone (35 c.c.) and water (9 c.c.) was refluxed with anhydrous potassium acetate (1·4 g.) for 9 hr. The solution was poured into water and the product isolated by means of ether. To ensure absence of acetate the product was refluxed with 5% ethanolic potassium hydroxide (20 c.c.) for 0·5 hr. Extraction with ether and working up in the usual way gave an oil (360 mg.), which was chromatographed on neutral aluminium oxide (Woelm; activity I; 11 g.). Elution with pentane (2 × 50 c.c.) gave cholesta-4 : 6-diene (49·5 mg.), m. p. 90°, $[\alpha]_D$ +4° (*c* 0·5), whilst elution with ether (2 × 50 c.c.) gave cholest-4-en-7β-ol (280 mg.), m. p. 121—124°, $[\alpha]_D$ +81° (*c* 0·82). No other product was isolated.

Reduction with lithium aluminium hydride. The toluene-*p*-sulphonate (500 mg.) in anhydrous ether (50 c.c.) was refluxed with lithium aluminium hydride for 17 hr. Working up in the usual way gave an oil (355 mg.), which was chromatographed on aluminium oxide (11 g.). Elution with pentane gave cholest-4-ene (300 mg.), m. p. and mixed m. p. 74—76°, $[\alpha]_D$ +58° (*c* 0·96); further elution with pentane gave an insignificant amount of material, whilst use of ether gave a trace of oil (7 mg.), and no detectable amount of cholest-4-en-7β-ol.

One of us (R. J. W. W.) gratefully acknowledges a maintenance grant from the Department of Scientific and Industrial Research.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA. [*Received, December 1st*, 1955.]

[3] Shoppee and Westcott, *J.*, 1955, 1891, and references there cited.
[4] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[5] Petersen and Chen, *J. Amer. Chem. Soc.*, 1955, **77**, 2557.

*The Photosynthetic Carbon Cycle.**

THE CENTENARY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY, IN THE ROOMS OF THE INSTITUTION OF CIVIL ENGINEERS, LONDON, ON OCTOBER 20TH, 1955, AND AT THE UNIVERSITY, GLASGOW, ON OCTOBER 28TH, 1955.

By MELVIN CALVIN.

SOME of you may have heard parts of this Lecture three or four years ago but it has materially changed since then in two ways. One is that we now know what the photosynthetic carbon cycle is, and it has been carried out, I can tell you now, in its entirety in the absence of living materials or formed parts of living cells. It has been carried out by a separate collection of soluble chemicals so that we are quite sure what it is, and now we can talk about it with a high degree of confidence.

When the work first began, we called it " the path of carbon in photosynthesis," which is a more or less general description of how carbon passes through the plant from the condition of carbon dioxide to the condition of carbohydrate. At the time that the title was invented we really did not know what kind of sequence of chemical transformations would be involved. One of the reasons that the title has changed from " the path of carbon " to " the photosynthetic cycle " is that now we know that it is a cyclic operation and that we can define exactly the compounds involved.

The discussion will be roughly divided into two fairly distinct parts: the first part involves the description of the set of chemical transformations which the carbon atom of carbon dioxide undergoes on its way from carbon dioxide to carbohydrate; and the second part describes the state of our knowledge of how the electromagnetic energy which is captured by the chlorophyll in the green plant is used to accomplish that series of transformations, since the series of transformations—carbon dioxide plus water to give carbohydrate and oxygen—is an upgrade one, that is, one in which energy is stored. That energy, ultimately, as we know, must come from the electromagnetic radiation absorbed by the chlorophyll.

Now, actually, the latter part of the discussion is on a different plane with respect to the degree of certainty than is the way in which the energy is used in transforming the carbon skeleton. I appraise you of this fact at the beginning so that you may be conscious of the transition some time toward the middle of this discussion.

This question of the biosynthesis of carbohydrate from carbon dioxide was originally the exclusive province of organic chemists. As a matter of fact, the founders of organic chemistry are rather closely associated with the early attempt to describe the biosynthetic mechanism of carbohydrate synthesis. Liebig, Emil Fischer, and, more recently, Willstätter and Stoll are very closely associated with the early attempts to describe the sequence of transformations that lie between carbon dioxide and carbohydrates. In general, these speculations were based upon structural analogies—upon the structural features of carbohydrates—and also upon certain kinds of deductions with respect to the nature of the reactions which the chemist could carry out and is familiar with in the laboratory. As it turns out, you will see that none of the speculations of Liebig, Fischer, or Willstätter has been substantiated, and in place of these we have discovered that the natural route by which carbon is converted from carbon dioxide into sugar is, in some senses, much simpler than the routes proposed by these earlier chemists and, in another sense, much more complex. Thus, the principles of the transformations are simpler, but the actual details of the transformations are more complex. I hope, perhaps, to be able to point out some of these things.

Willstätter and his predecessors were confined more to structural analogy in their attempts to devise a biosynthetic route. We were much more fortunate—roughly 40 years later—because we have in our hands a method of examining the detailed stages of the transformation which is independent of structural analogy. This method depends upon the availability of tracer carbon, that is, a long-lived radioactive carbon. This one happens to be ^{14}C which has a half-life, as you know, of 5000 years so that there is ample time, although I must admit that at the beginning of this work it looked as though we might not have plenty of time. The method, in principle, was very simple. We knew that the green plant absorbs carbon dioxide and ultimately, through the agency of the absorbed light, causes it to react with water, or the elements of water, and finally to produce carbohydrate. We know this much: but we didn't know what lay between

* The work described in this Lecture was sponsored by the U.S. Atomic Energy Commission.

the two ends, and in principle it became a straightforward matter to feed the plant with labelled carbon dioxide and take a series of time snapshots as the carbon passes from carbon dioxide into the plant through all the chemicals that it has to go through and arrives in carbohydrate. It is clear that there must be a sequence of intermediates—the early ones should become labelled first and the later ones later, and eventually, of course, the label will appear in carbohydrate. So the principle of what I will call "appearance-rate experiments" is perfectly straightforward. These were the first types of experiments which we performed.

We set up a plant in what we may call a "steady state" of photosynthesis: that is, the plant was absorbing carbon dioxide, light, and water, and ejecting, or, if you like, throwing off oxygen and storing away carbohydrate; this is a "steady state." Carbon is coming in at one end and the carbohydrate is being deposited at the other, and in between—or somewhere along the line—oxygen is evolved. Now, at a given instant of time we inject into the incoming stream of carbon, labelled carbon atoms in the form of labelled carbon dioxide. Then we take a series of photographs in time of the chemical distribution of the radiocarbon as it passes into the plant. We will then have performed, in essence, the basic experiment of an appearance-rate curve. The problem, of course, is, first, to select the proper biological material, and, secondly, to devise a method which will give us the proper photograph of the distribution of the radiocarbon in the plant. The first of these was practically determined for us. There was little choice remaining because of the highly developed state of knowledge of algal growth. Two requirements were determining. One was the desire we had to handle the biological material as nearly as possible in the same way as chemicals. One cannot do that with an entire plant but one can with a bottle of algæ; one cannot treat it quite like a bottle of chemicals off the shelf, but this was our predisposition and for this reason we used algæ primarily for our early experiments. The second factor was that the algæ which we used had been used previously in a wide variety of photosynthetic experiments, so that the general technique of growing them in a small way had been already developed. We had to develop it much further because our method of examining the algæ was much more precise and more detailed than had previously been used. Therefore, algæ that were grown in batches each day were not good enough for our purposes. We soon found out that they were not chemicals—that they varied from day to day if good care was not taken of them—and it became necessary for us to provide our own algæ farm in which we grew the algæ under extremely closely controlled conditions so that the suspension of the algæ that we used each day would do the same thing each day. This was, you might say, an elementary requirement of scientific investigation—that the bottle which you believed to be the same shall actually be the same. As I said, it required the development of our highly controlled algæ farm and we have been improving it ever since as our methods of investigating the product became more delicate and more precise.

Of course, we begin to detect variations even in the algæ of today and we have to continue to improve their culture. Another sort of thing which we have done, I might say, is to use a wide variety of plants, and the conclusions which we have drawn with algæ we have been able to demonstrate throughout the plant kingdom—in fact, from the blue-green algæ which are very closely related to bacteria through plants such as the mosses and grasses, to the leaves of the higher plants.

The plant material having been selected for our major work, namely, the algæ, it was easy enough to set them up in a steady state of photosynthesis and then to take little samples of them at various intervals of time after the radiocarbon had been introduced and drop them into boiling alcohol which, in effect, stops all the biological reactions, destroying the activity of the enzymes involved in the reactions. Then it became necessary for us to devise a method of analyzing the extract that was so produced.

These extracts were first mixture-extracts—made by extracting first with 80% alcohol, then with 20% alcohol. Some of the materials were soluble in the 80% alcohol which was the original solution. Then it turned out that a good fraction of what we wanted was not as soluble in 80% alcohol as would be desirable, and the second extraction of the material was made with 20% alcohol. The two extracts were put together and the analysis made of the mixture. In the beginning we used classical organic analytical methods. We attempted to extract each compound that was present in macroscopic amounts—to purify it, crystallize it, and to measure its radioactivity. This was a very laborious procedure, and after a couple of years we identified one compound and it had only a small fraction of the total radioactivity that was in this plant after a minute or two. It was quite clear that we had to devise something more rapid—a general method of analysis—and this led to a combination of the elegant method of paper chromatography which had been developed for the analysis of protein hydrolysates in

FIG. 1.

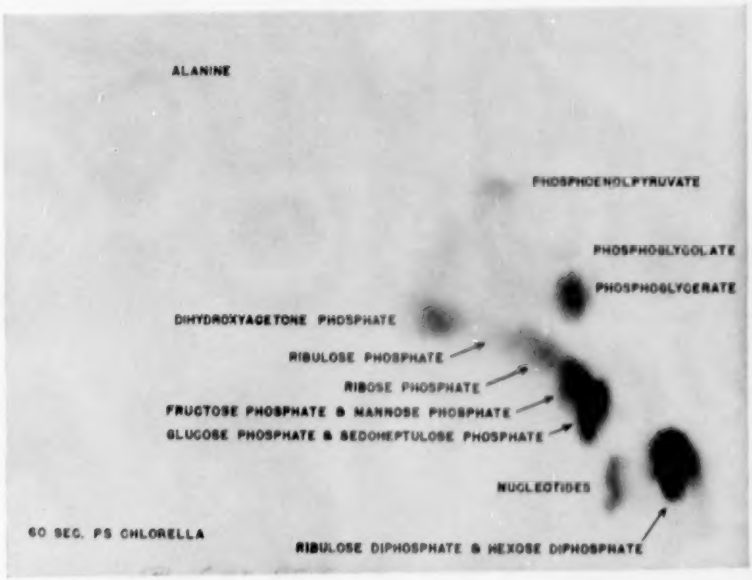
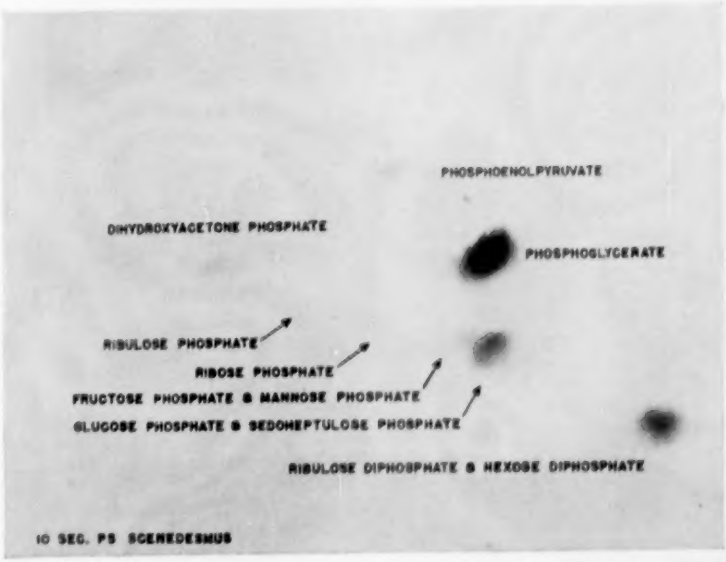


FIG. 2.



FIGS. 1 *and* 2. *Chromatogram of extract from algæ indicating uptake of radiocarbon during photosynthesis by* (*Fig.* 1) Chlorella (60 *seconds*) and (*Fig.* 2) Scenedesmus (10 *seconds*).

[*To face p.* 1896.

FIG. 14. *Chromotograms showing effect of enzyme action on ribulose phosphate.*

England together with our method of examining the extracts for radioactivity. The two things together provided us with an extremely rapid, general, and useful tool for the analysis of the extract. The principles of two-dimensional paper chromatography have been amply described elsewhere and will not be repeated here.

We are not interested in all of the compounds in the extract. We are interested only in those which have radiocarbon in them. I might say the amount of material we put on the paper is so small that, in general, when the chromatograms are made the dried paper looks just as it did at the beginning, except for small pencil marks where the original spot was. The chlorophyll actually is often visible on the paper, but most of the paper is quite colourless. We do not know what compounds we are looking for, not even their chemical nature, so we could not examine the paper by ordinary chemical means—that is, by colour tests—the only thing that characterizes them with certainty is the radioactive carbon content, and those are the ones in which we are interested. This, of course, makes it very simple—we need no chemical spray to find the compounds we want on the paper. All we have to do is find where the radioactive areas are, on the paper, which will then locate the compounds in which we are interested.

There are several ways in which this can be done. One is to put a small boy to work with a Geiger counter and have him explore the paper inch by inch, and we do that occasionally when we have a great deal of time or when we know approximately where to look. But the best way has turned out to be to place an *X*-ray film in contact with the paper, of the same size as the paper, and wherever there is a radioactive spot the *X*-ray film will be exposed. Before the exposure, we place a radioactive mark at two corners of the paper so that the relation of the film to the paper can be reproduced. Then we develop the film after a suitable length of exposure and get a series of dark spots on the film for the particular compounds in which we are interested.

The next problem is the identification of the chemical character of each of these areas. Here we begin to use our information as to the relation between the chemical structure and how the compounds migrate—that is our first approximation. Then we use the more general technique of cutting out the radioactive spots of the paper, eluting them with a suitable solvent, performing a chemical operation on the resulting 0·2—0·3 c.c. of solution, then putting it back on paper and again running the paper in two-dimensional chromatography. From the behaviour before and after the chemical treatment and the location of the material in each case, we eventually can narrow down the chemical character of the material, and the final identification of the material is achieved by mixing with the radioactive material the supposed chemical which it is, in an amount sufficient to give a colour test. By that time there will already be enough information about the chemical character to have devised a suitable colour test for it on the paper and then to show the absolute coincidence of the radioactivity and the colour test. The amount of chemical which is extracted from the plant and is radioactive is negligible compared with the amount we add for the chromatography, so that the colour test is given only by the material which we add. Radioactivity is given only by the material which was extracted from the plant and the two things coincide exactly; not " nearly " in the centre of gravity of the spots but in the shape—the spots are never simple, they have very irregular edges. The two things have to correspond exactly in every respect before we consider the identity of compounds established.

This, then, is the general analytical technique. The results of the first experiments are shown in the first two Plates. Fig. 1 shows the result of a 60-sec. exposure; this happens to be for one type of alga; the black spots that we get are clearly separated. In 60 sec. there are perhaps a dozen or more compounds formed with radiocarbon in them and some of them contain large amounts of radiocarbon; so from this alone we recognize that 60 sec. is much too long.

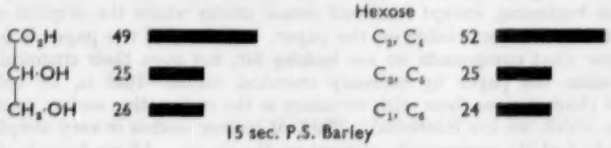
Now Fig. 2 shows a much shorter exposure time of 10 sec. with different but very closely related algæ. To a chemist they are very much alike, but it turns out that for other purposes—we will see later in the discussion—the difference between these two organisms has become of significance. For the most part the earlier compounds have disappeared and one compound has become predominant, namely phosphoglyceric acid. When this was done on as quantitatively kinetic a basis as we could later do it, and a plot was made in terms of percentage of the total radioactivity which occurs in each compound, and this percentage then extrapolated back to zero time, this compound (phosphoglyceric acid) does indeed extrapolate to very nearly 100%.

Now phosphoglyceric acid (PGA) is a compound which contains three carbon atoms, and the next question that arises is which of the three carbon atoms contains the greatest amount of radioactivity. This was established by breaking the acid apart by established chemical

methods, so that we knew precisely which carbon atom was which, in a separated form. This was done, with the result shown in Fig. 3.

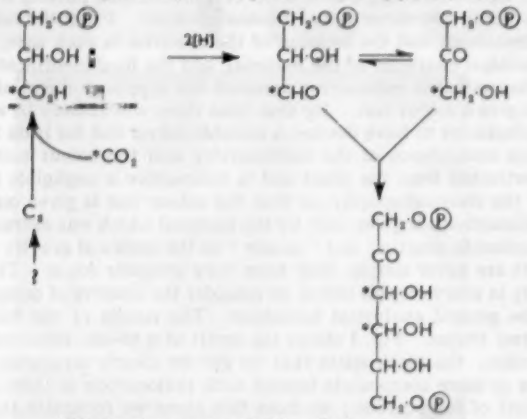
This shows the distribution of radioactivity in the three carbon atoms; it is a 15-second photosynthetic experiment in barley. Actually, it looks as though I have done this with a purpose : there are three different plants here; that is, *Chlorella* on the first figure, *Scenedesmus*

FIG. 3. *Distribution of labelled carbon in photosynthesis experiments.*



on the second, and barley on the third. I assure you this was quite accidental; I didn't pick them out to have three different organisms. But it does illustrate the basic point I tried to make earlier, namely, that the fundamental conclusions which were drawn have actually been checked with about twenty different plant materials and they differ only quantitatively—qualitatively they are the same. Notice that the distribution of the carbon in glyceric acid from 15-seconds photosynthesis in barley shows most of the radioactivity in the carboxyl group and the rest of it equally distributed between $C_{(\alpha)}$ and $C_{(\beta)}$. From the same experiment we extracted some hexose and degraded it, and here you notice that the distribution of radioactivity is such that it appears that the middle two carbon atoms of the hexose are formed from the carboxyl group of the glyceric acid and the outer four correspond to the α- and β-carbon atoms of the glyceric acid. This very early finding suggested immediately that the hexose was made by a reversal of the well-known glycolytic fission of the six-carbon piece into two three's, in such a manner that the middle carbon atom arises from the carboxyl group of the phospho-

FIG. 4. *Path of carbon from CO_2 to hexose during photosynthesis.*



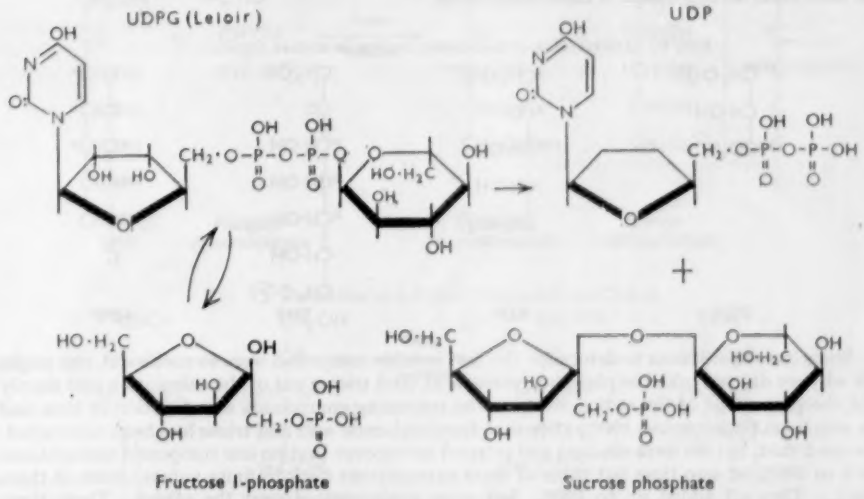
([H] denotes some available reducing agent.)

glyceric acid which is just reduced to an aldehyde group. I might say that this has since been confirmed in a variety of ways and the detail of this relation is shown in Fig. 4, in which the phosphoglyceric acid is shown as first reduced with two equivalents of reducing agent to form labelled glyceraldehyde. There is one point that must now be emphasized, namely, that as the time is shortened the radioactivity appears more and more in the carboxyl group of the glyceric acid. So in the very shortest times which we have been able to use it is practically all in the carboxyl group and none in the α- or β-carbon atom.

Fig. 4 shows the relation of the glyceraldehyde to the corresponding keto-triose which then come together head-to-head, to form the hexose with the two erstwhile carboxyl carbon atoms in the middle. It is the well-known aldolase fission of fructose diphosphate in the reverse direction, which is well established in yeast, and now we have it going forward in the green

plant—at least from the phosphoglyceric acid to fructose diphosphate. The fate of the fructose diphosphate has been elaborated further since most of the carbon eventually shows up in some form of free carbohydrate. As a matter of fact, in most of our plants it shows up first as sucrose itself. It became of interest to us to see if we couldn't find out how sucrose was made from fructose diphosphate. This turned out to be not too difficult after some of our additional spots had been identified. One of them, namely, the uridine-diphosphoglucose (UDPG), turned out to be of great importance. When we recognized it, we knew only that it was one of the very early labelled compounds and labelled only in the glucose moiety. The questions how it got there and what its fate was immediately arose and we suggested an answer which has since been confirmed by individual enzymic experiments by Leloir. The chemical and how it is used are shown in Fig. 5.

FIG. 5. *Uridine-diphosphoglucose reaction with fructose diphosphate.*



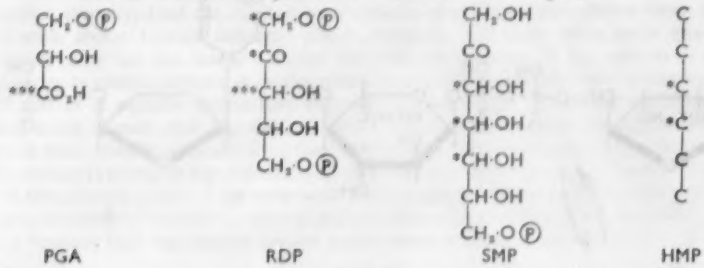
The first unphosphorylated carbohydrate compound that we could identify was sucrose and, therefore, it became necessary for us to devise a way of going directly from the phosphorylated hexoses to sucrose. Now one of the early intermediates which we identified was uridine-diphosphoglucose, and the label was all on the glucose. This is a very labile compound; it is extremely easily hydrolyzed to free glucose. It is one of the few glucose compounds that is more easily hydrolyzed than glucose 1-phosphate. We suggested, since we saw no free labelled hexose, that is, no unphosphorylated hexose, that the sucrose was synthesized by an exchange reaction between the glucose of uridine-diphosphoglucose and the proton of the 2-hydroxyl group of fructose 1-phosphate to form urdine diphosphate and sucrose phosphate. Now the phosphorus is at position 1 of the fructose moiety and then this loses its phosphate to yield sucrose.

As I said earlier, this basic notion has since been confirmed by Leloir who has prepared enzyme extracts which will carry out such reactions. The first which he found used, not fructose phosphate, but fructose itself and uridine-diphosphoglucose to make sucrose directly, and more recently he has found an enzyme system which will catalyze the reaction of uridine-diphosphoglucose with fructose phosphate to make a sucrose phosphate. I might say that we had also found sucrose phosphate in the plant, although in extremely minute amounts. Thus, we have completed the sequence from carbon dioxide all the way to the major product, sucrose, beginning with phosphoglyceric acid as the first identifiable compound isolated from the plant.

Now a glance at Fig. 4 implied that the reaction was such as to indicate that something must combine with the carbon dioxide to make directly carboxyl-labelled phosphoglyceric acid. The arithmetic suggests that this something should be a two-carbon compound or one which yields a two-carbon compound extremely easily. In the search for that precursor to phosphoglyceric acid—that acceptor of carbon dioxide which leads to phosphoglyceric acid—we identified

everything but a two-carbon compound. Instead of finding it, we found a five-carbon sugar, ribulose diphosphate (RDP), and a number of related five-carbon sugars, ribose 5-phosphate and ribulose 5-phosphate (Fig. 6). We found, still more surprisingly, the seven-carbon sugar, sedoheptulose monophosphate (SMP). There is also sedoheptulose diphosphate present, but ribulose diphosphate and sedoheptulose monophosphate are the compounds which are present in largest amounts, although the diphosphate of the C_7-sugar and the monophosphate of the C_8-sugar are also present. Of course, we found, in addition to fructose diphosphate, fructose monophosphate, glucose monophosphate, and mannose monophosphate : these are all to be understood in Fig. 6 in the group of hexose monophosphates (HMP). But no two-carbon pieces appeared that might conceivably be progenitors of the α- and β-carbon atoms of phosphoglyceric acid. Obviously, it became necessary for us, not only to identify these compounds and to get their appearance curves as whole compounds, but also to go much further than that : actually to degrade all of these compounds, one carbon atom at a time, and draw appearance curves of the individual carbon atoms in these compounds.

FIG. 6. *Distribution of radioactive carbon in certain sugars.*



Since our experiments to determine the first isolable compound were so successful, one might ask why we did not take the phosphoglyceric acid (and triose) out of the calculation and simply plot the percentage of the radioactivity in the remaining compounds as a function of time and see which next approached 100% after the phosphoglyceric acid and triose had been subtracted. We tried that, but we were shocked and puzzled to discover that no one compound extrapolated back to 100% at zero time but three of them extrapolated back to finite values—none of them 100%. They all added up to 100%, but none predominated over the others. These three were the pentose, the heptose, and the hexose, and we could not distinguish one as dominant over the others. You will note later why that situation arose. The simple appearance-curve analysis broke down and it failed us on the very next step of the analysis. Even when we proceeded to the individual carbon atoms, it failed us. We could notice as we analyzed the distribution of carbon in these four compounds, including phosphoglyceric acid (see Fig. 6), which seem to be the basic ones of the whole group, that there were very peculiar relations between them. The stars represent the approximate degree of relative radioactivity among the carbon atoms in each of these compounds. I shall not go through the very complex and rather involved detailed arguments which permitted us to determine the relations between these compounds. You will note that there is no simple relation between them; *e.g.*, the five-carbon fragment does not appear with this distribution anywhere in the seven- or the six-carbon materials; the six-carbon fragment does not occur with its own distribution anywhere in the seven-carbon material; in fact, there is no simple relation but we were able to devise an unequivocal relation between them by careful analysis of the kind that led to the establishment of the relation between the triose and the hexose. We were able to establish the connection between the hexose, the pentose, and the heptose. Figs. 7 and 8 show the relations we were able to deduce.

Fig. 7 shows the route of formation of the pentoses. The right-hand symbol is the distribution of the label that we find in the pentose, and once we realized that the pentose (ribulose diphosphate was what we were analyzing) might possibly arise from two different sources it became possible for us to devise a unique scheme which would give it. This, then, provides the source of the pentose—the triose to which the top two carbon atoms of the heptose have been added to give two pentoses, *viz.*, ribulose 5-phosphate, which comes from the top two carbon atoms of heptose plus the triose, and the ribose monophosphate which comes from the

bottom five carbon atoms remaining from the heptose. The two together then are both converted into ribulose diphosphate and the analysis of the ribulose diphosphate, which is what we performed, gives the distribution which we found. While this is fine—it gives us the relation between the pentose, the triose, and the heptose—we still have to devise a way of creating the heptose. Now notice that we cannot create that heptose from pentose because we are using it to make pentose. So we have to devise another way of making the heptose. There is only a limited number of ways in which this can be done. It could be made, presumably, from hexose plus one carbon atom, but there is no way in which to make it from one carbon atom and hexose with the type of label which we have. If that were the case—if that one carbon atom were to come from carbon dioxide—then eventually, in the shortest possible time, in the heptose there should appear at least one carbon atom which is " hotter " than all the others, and this was never the

FIG. 7. *Formation of five-carbon sugars from sedoheptulose phosphate* (SMP).

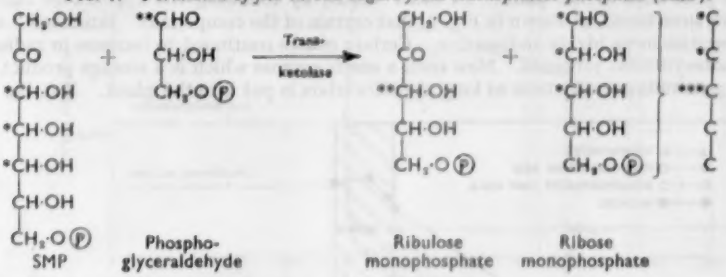
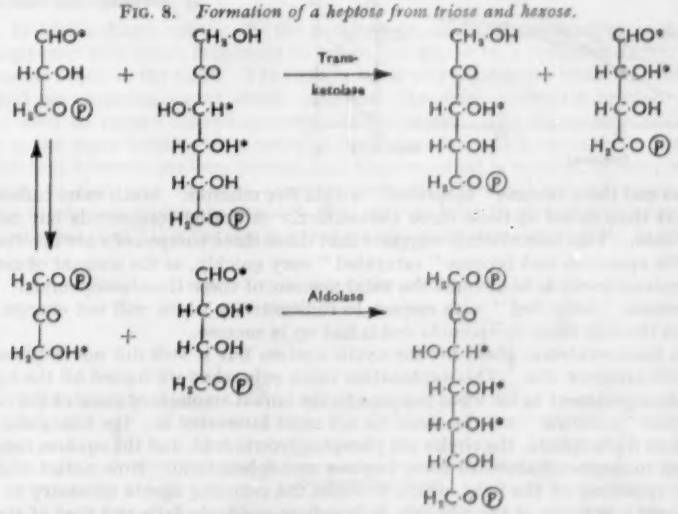


FIG. 8. *Formation of a heptose from triose and hexose.*



case; even in a fraction of a tenth of a second the heptose had the distribution shown. If anything, $C_{(3)}$ and $C_{(5)}$ were always equally labelled (or very nearly always equally) and $C_{(4)}$ less so at the shortest times (a fraction of a tenth of a second). So we had to devise another way of making this heptose and there is only one way left. If one may not use either the hexose and a one-carbon fragment, or the pentose and a two-carbon fragment, one must make it from a tetrose. If one makes it from the tetrose, the other part must be a triose—and we have plenty of triose. We now have the problem of making a tetrose with the proper labelling. Fig. 8 shows how this can be done.

We take the same reaction which we used to make the pentose from the heptose: the top two carbon atoms of the keto-hexose added to triose make another pentose and a tetrose with the required type of labelling. This tetrose, then, combines with the triose to make (with the

same enzyme which makes the hexose from two trioses, that is, one ketose and one aldose) the heptulose diphosphate with the distribution we need. This, then, is the source of the heptose. Again it comes from hexose and triose *via* the reactions of Fig. 8. I might say that as this work progressed, as we devised these schemes and came to the conclusion that this must be the way in which these compounds are formed, the enzymologists shortly after our discovery of the universal appearance of the seven-carbon sugar in all plants, found it also in animal tissue and then they proceeded to search for the enzyme that would do this reaction—and, indeed, they found it. All of these reactions have now been carried out as separate reactions by suitable enzymes. Thus, we now have found the relation between the triose, pentose, heptose, and hexose, but none of this had led us to the answer we were seeking, namely, the precursor of the phosphoglyceric acid.

This required a different type of experiment, in which the radioactivity was used to determine the total pool sizes in the plant. In other words, by following the appearance curves long enough we have found, as shown in Fig. 9, that certain of the compounds " saturated " and then did not become more highly radioactive. Certain others continued to increase in radioactivity as the photosynthesis proceeds. Now such a one is sucrose which is a storage product (an end product); its radioactivity rises as long as radiocarbon is put into the plant. But the activity

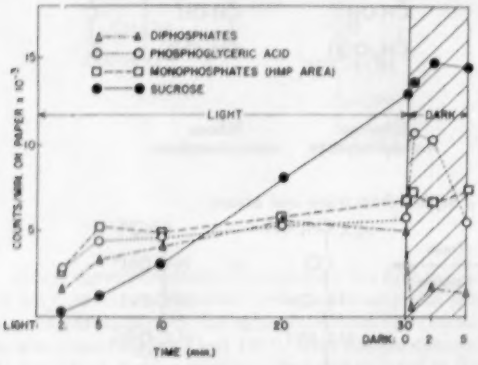


FIG. 9. *Effect of light and dark on activities of phosphates and sucrose.*

of others rises and these become " saturated " within five minutes. Much more carbon has gone into the plant than exists in these three radioactively saturated compounds but most of it is stored in sucrose. This immediately suggests that these three compounds are involved in some sort of a cyclic operation and become " saturated " very quickly, as the amount of carbon going through to sucrose exceeds in amount the total amount of these three compounds. They will, of course, become " saturated " with respect to radioactivity which will not change further as carbon passes through these compounds and is laid up in sucrose.

This was more evidence, then, for the cyclic system but it still did not explain what the carbon dioxide acceptor was. This explanation came only when we turned off the light in such a steady-state experiment to see what happens to the actual amounts of some of the compounds. Now these that " saturate " are the three we are most interested in; the triangular points are mostly ribulose diphosphate, the circles are phosphoglyceric acid, and the squares consist mostly of the hexose monophosphate with some heptose monophosphate. Now notice what happens on suddenly switching off the light, which provides the reducing agents necessary to reduce the carbon to sugar: activity of the ribulose diphosphate suddenly falls and that of the phosphoglyceric acid suddenly rises. Now it is already clear that the triose has its origin in the phosphoglyceric acid by reduction, and as soon as the light is removed reduction of glyceric acid to glyceraldehyde ceases. So the activity of the acid starts rising, but the corresponding fall in the ribulose diphosphate focused our attention on this as the possible source of the two carbon atoms, *i.e.*, of the precursor of the phosphoglyceric acid. The fact that this diphosphate activity fell by approximately the same amount as that of phosphoglyceric acid rose suggested that the two were closely related, and that in the way that we needed to make ribulose diphosphate the carbon dioxide acceptor and its five carbons plus one carbon dioxide molecule make two phosphoglyceric acid molecules. Now this completes a cyclic sequence which will be shown diagrammatically below.

Fig. 9 is included more or less for historical purposes because it is the first run of this sort

which focused our attention on ribulose diphosphate as a carbon dioxide acceptor. Since that time we have done the experiment again and Fig. 10 is a nice illustration of what happens when you know what you have. It shows the same experiment done two years later : here the ribulose diphosphate activity falls and the phosphoglyceric acid activity rises, beautifully confirming the original experiment in which there were only one or two points but from which we made the proper guess.

FIG. 10. *Light–dark transients in phosphoglyceric acid and ribulose diphosphate activities.*

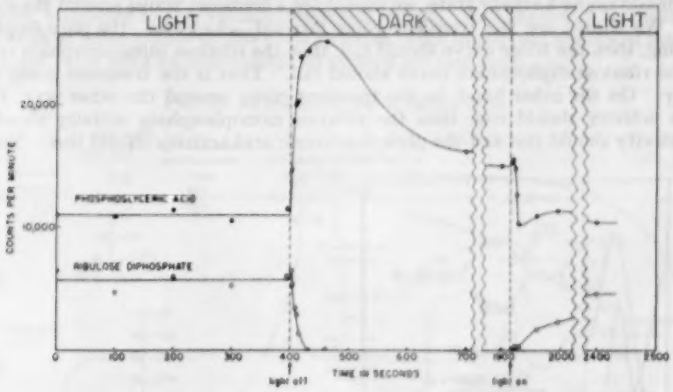
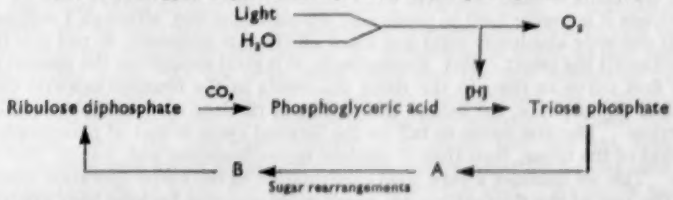


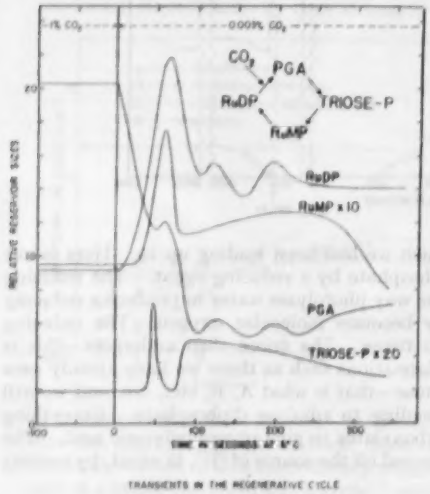
Fig. 11 shows diagrammatically the cycle which we had been leading up to. Here is our phosphoglyceric acid which is reduced to triose phosphate by a reducing agent. The reducing agent has its origin in the light. The light in some way photolyzes water to produce a reducing agent and an oxidizing agent which ultimately becomes molecular oxygen. The reducing agent is used to reduce phosphoglyceric acid to triose. The triose then undergoes—this is already at the sugar level now—a series of transformations such as those we have already seen in the relation between pentose, hexose, and heptose—that is what A, B, etc., are, and we will come back to that in a moment—eventually leading to ribulose diphosphate. Everything builds up to ribulose diphosphate which then carboxylates to give phosphoglyceric acid. The light experiment (Fig. 11) is the one in which we turned off the source of [H], in effect, by turning

FIG. 11. *Suggested cyclic scheme for relations in photosynthesis.*



off the light. We block that point of the cycle and what has happened is that phosphoglyceric acid has built up and ribulose diphosphate has fallen, because if reduction of phosphoglyceric acid is blocked there is no source for the ribulose diphosphate but the carbon dioxide is still there to carboxylate it to give phosphoglyceric acid. This immediately suggests another type of experiment to check this simple diagrammatic cycle. There are two points at which we get into this cycle as far as this diagram is concerned. We can get into it, or effect it, by changing the level of reducing agent and that is what we did by changing the light—we can get into it by changing the level of carbon dioxide, keeping the illumination constant. This is the other possible way in which we can induce transients in these pools. We did that experiment : it is much more difficult to do but it has been done. The predicted result is that ribulose diphosphate activity should build up and that of phosphoglyceric acid decrease in the initial phases of that transient. We cannot see easily what happens afterwards, as will be discussed below.

Fig. 12 shows the results of such an experiment, showing the effect of dropping the carbon dioxide pressure from 1% to 0·003%. Now it takes a few seconds actually to get the carbon dioxide out of the system—to change it (it is not like light which can be turned out). So the Figure shows that our prediction is fully borne out. The first thing that happened after the carbon dioxide dropped was that the phosphoglyceric acid curve fell. On the other hand, the ribulose diphosphate curve rose, as predicted. This Figure actually contained a lot more information than that. If these things are related in a cyclic system as we had proposed and we suddenly throw into this cyclic system a change of one of the external conditions, which is involved in maintaining a steady state, we should see a transient travel around the cycle in both directions. We should see the transient going forward—clockwise—the phosphoglyceric acid curve is falling, then the triose curve should fall, then the ribulose monophosphate curve should fall, then the ribulose diphosphate curve should fall. That is the transient going around the forward way. On the other hand, in the transient going around the other way, the ribulose diphosphate activity should rise, then the ribulose monophosphate activity should rise and the triose activity should rise and the phosphoglyceric acid activity should rise. Now this pair



TRANSIENTS IN THE REGENERATIVE CYCLE

Fig. 12. *Transients in the regenerative cycle.*

of transients travelling around the cycle will eventually meet and there is then an oscillation. After the first one it is pretty hard to predict by simple inspection, although I suppose it would be possible, if one were absolutely right and knew all the rate constants, to put this thing into a calculator and await the result. But, qualitatively, it is good enough for the present purpose.

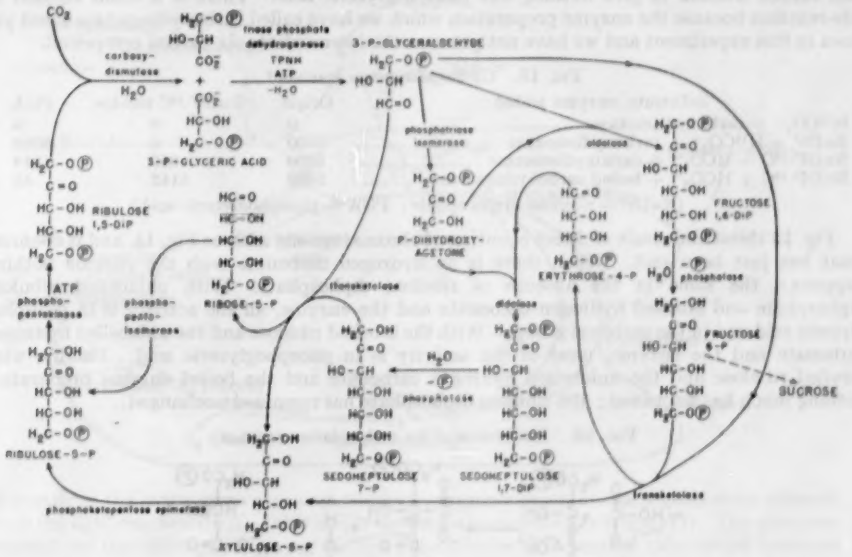
Now the first curve to rise—in the rising transients in the counterclockwise direction—is that of ribulose diphosphate, the second thing, that of ribulose monophosphate, and the third that of the triose. The first curve to fall on the forward cycle is that of phosphoglyceric acid, the second that of the triose, then that of ribulose monophosphate and, finally, that of ribulose diphosphate. This we consider a very good confirmation of the cyclic operation which we have proposed. The rest of the fluctuations are much more complex because they are interrelated, now, with the take-offs from this cycle, and these things are for further investigation. The method, I think, is established and is a very powerful one in examining the interrelations of a complex system of this sort.

The details of the sugar transformations leading to the carboxylation of ribulose diphosphate we have already seen, so that we can now set up the entire cycle (Fig. 13). It contains all of the elements which we have discussed one at a time up to now. It contains the formation of the phosphoglyceric acid from ribulose diphosphate and carbon dioxide, also the reduction of the phosphoglyceric acid to phosphoglyceraldehyde; then the phosphoglyceraldehyde undergoes four different reactions in parallel. That is why we never see (as mentioned earlier) a second compound as the successor to phosphoglyceric acid (and triose). The steady-state level of triose was so small that we could seldom use it. We had to use things like the hexose, the pentose, and the heptose, and these all come in later. The triose and the hexose make the

tetrose and the pentose; the tetrose and the triose then get together to make the heptose almost certainly as the diphosphate, which then loses one phosphorus atom to make the heptose monophosphate, which then undergoes the same transketolase reaction as the first one—the top two carbon atoms of the heptose combining with triose to make the two pentoses. Now these reactions in all cases lead to ribulose 5-phosphate which finally requires another phosphorus atom at position 1 to make the 1 : 5-diphosphate. Thus, we are back again to a system capable of carboxylation.

This, then, is the entire cycle. One starts with one each of these molecules and then by going around the cycle six times ends with one extra hexose molecule which we can now take off to form sucrose, according to the reaction developed earlier. As a matter of fact, carbon can be taken off at various other points of this cycle to make other important biological materials, but this is the major route from carbon dioxide to sucrose *via* this cycle.

FIG. 13. *The photosynthetic carbon cycle.*



There is one other thing to mention in connection with this cycle—it completes the story. As stated above, the aldolase reaction (and isomerase reaction) had been known ten to fifteen years ago, in connection with the reverse process, the breakdown of sugar, so that they were well known as individual steps. As the work went along and the new substrates (ribulose and sedoheptulose) were discovered and the relations between them defined, the enzymes responsible for the required reactions were partially purified by the enzymologists. About the time when we finally decided what the new carboxylation was, which had not yet been described enzymically, it seemed wise for us to become enzymologists at least for a short time and try to demonstrate this reaction in a cell-free system. And we did that. We made extracts from both algæ and spinach and we got our ribulose diphosphate out of the plant by paper chromatography and cutting out the proper areas of the paper. This was the quickest way to get it rather than to try to synthesize it; it has not been synthesized yet. We tested the extracts for this reaction. It was all done by our technique of chromatography with radioautography. I might say, first, that if we used unlabelled ribulose diphosphate and labelled carbon dioxide in our reaction mixture and put the enzyme in, then all we got was labelled phosphoglyceric acid. But this could have happened in a variety of ways. The phosphoglyceric acid so obtained was carboxyl-labelled. Now we wanted to do it the other way. We wanted to take labelled ribulose diphosphate, so that we would know exactly what happened to all those five carbon atoms, and then unlabelled carbon dioxide and the enzyme and see what happened. That should make phosphoglyceric acid, of which one molecule was labelled equally in all three (starting with uniformly labelled rubulose) carbon atoms and it should make one phospho-

glyceric acid which was labelled only in the bottom two and not in the carboxyl group, so that the average of the two would be that the carboxyl was slightly less radioactive than the other two, instead of the opposite as in the first experiment. Fig. 14 (Plate facing p. 1897) shows the kind of data obtained; we see what happens with labelled ribulose diphosphate, unlabelled sodium hydrogen carbonate, and enzyme; phosphoglyceric acid is formed—some of the ribulose diphosphate is not used. It is a short time—I think it is only about a two-minute experiment—two minutes' exposure to (unlabelled) sodium hydrogen carbonate in these three chromatograms. There is apparently some enzyme in this preparation which converts some of the ribulose diphosphate into ribulose monophosphate, but most of it becomes phosphoglyceric acid. If the hydrogen carbonate is omitted, no phosphoglyceric acid is formed. This is the important thing. It is the hydrogen carbonate which does it; and if the enzyme is omitted nothing happens—one has just the ribulose diphosphate (with some ribulose monophosphate which is present in the sugar preparation). So we have demonstrated this reaction—ribulose diphosphate plus carbon dioxide to give nothing but phosphoglyceric acid. There is a small amount of side-reaction because the enzyme preparation which we have called carboxydismutase is not yet clean in this experiment and we have not yet seen the intermediate six-carbon compound.

FIG. 15. *Carboxydismutase reaction.*[9]

Substrate, enzyme added	Origin	RuDP-^{14}C residue	PGA
$H^{14}CO_3^-$ + carboxydismutase	0	0	0
RuDP + $H^{14}CO_3^-$ + carboxydismutase	6000	0	6000
RuDP-^{14}C + HCO_3^- + carboxydismutase	5600	639	4218
RuDP-^{14}C + HCO_3^- + boiled carboxydismutase	5600	5142	58

(RuDP = ribulose disphosphate; PGA = phosphoglyceric acid.)

Fig. 15 shows the result of direct counting of chromatograms such as Fig. 14, and it confirms what has just been said. When there is no hydrogen carbonate with the enzyme nothing happens: the same in the absence of ribulose diphosphate. With unlabelled ribulose diphosphate and labelled hydrogen carbonate and the enzyme, all the activity is in phosphoglyceric acid and in the carboxyl group. With the labelled ribulose and the unlabelled hydrogen carbonate and the enzyme, most of the activity is in phosphoglyceric acid. Finally, with labelled ribulose and the unlabelled hydrogen carbonate and the boiled enzyme preparation nothing much has happened; the ribulose diphosphate has remained unchanged.

FIG. 16. *Mechanism of the carboxylation reaction.*

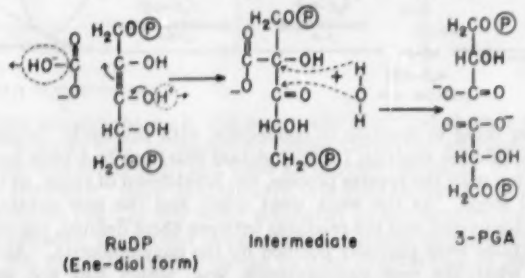
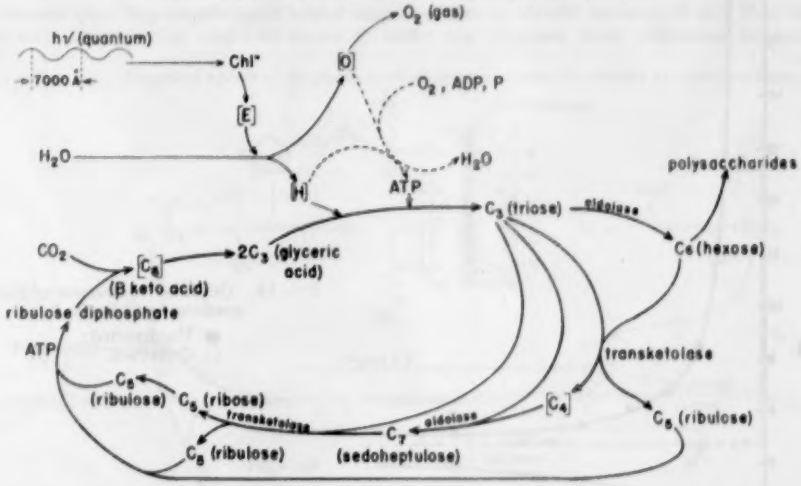


Fig. 16 gives a suggested mechanism for this carboxylation. The ribulose diphosphate in the enediol form can pick up bicarbonate ion with the elimination of the elements of water. This water molecule then can attack the resulting α-hydroxy-β-keto-acid in a standard fashion to hydrolyze it between the α- and the β-carbon atom and give two molecules of phosphoglyceric acid. We have never seen this intermediate and I think you can see why we would never see it under our isolation conditions. It would either be decarboxylated back to ribulose diphosphate, being an α-hydroxy-β-keto-acid, or it would be spontaneously hydrolyzed non-enzymically to give phosphoglyceric acid. This would be all we would see on our chromatograms. It is probably worthwhile hunting for this C_6 acid as an intermediate. Maybe one day somebody will do it.

We know now every step in the carbon cycle and I might add, parenthetically, that the entire cycle has been carried out in a soluble system. It has been done in a flask, so to speak, with a mixture of soluble enzymes and reagents. One feeds in carbon dioxide and takes out glucose, and this can be done now without the presence of any of the organized structures of the cell,

such as plastids, mitochondria, etc. Only soluble substances have been used, such as protein molecules and reagents—no organized particulate structures. This is not a light reaction because the reducing agent is supplied in the form of reduced pyridine nucleotide and the phosphorus is supplied in the form of adenosine triphosphate (ATP). Fig. 17 shows the photosynthetic cycle in a schematic way but emphasizes more the reagent requirements. It will be noted that all that is required to make it go are some reducing agents and some adenosine triphosphate (ATP). We need this triphosphate to make 1 : 3-diphosphoglyceric acid and to make ribulose diphosphate, and we need reducing power to reduce the glyceric acid (diphosphate). Those are the only two chemical reagents that are required to convert carbon dioxide into sugar. Now as stated above, this has actually been done by supplying the reducing agent in the form of reduced nucleotide and adenosine triphosphate as such, as indicated by Racker.[6]

FIG. 17. *Proposed cycle for carbon reduction in photosynthesis.*



Normally in the living green organism these two reagents must, of course, find their ultimate origin in the light reaction itself. This also is shown diagrammatically in Fig. 17. The quantum is absorbed by the chlorophyll, giving excited chlorophyll. The excited chlorophyll molecule then goes through some sort of an energy transformation, as yet unknown, to a situation (labelled [E] in Fig. 17), which ultimately uses that energy to split the water molecule into a reducing agent, [H], and some sort of an oxidizing agent [O]. The oxidizing agent eventually can rearrange itself and come out as oxygen gas. The reducing agent can be used to reduce the glyceric acid. In addition to that, we must supply the adenosine triphosphate. Now the way—one way at least—in which we know that large amounts of adenosine triphosphate can be made is by the combination of a reducing agent such as the pyridine nucleotide either with molecular oxygen or with some intermediate on the way to oxygen. We can now define the precise quantitative requirements for the reduction of *one carbon dioxide molecule*. We can say it requires four of these reducing hydrogen atoms and we can show that what is required are three molecules—at least three—of adenosine triphosphate. If these are the reagent requirements to run this cycle and these reagents must have their ultimate origin in a photochemical reaction, the question arises how can these two things be produced by the photochemical reaction. In general, the high-energy phosphate, as stated above, can be produced—and we know of several such methods of producing it—by some oxidation reaction. Now the oxidation can use pyridine nucleotide as substrate, can use molecular oxygen as the oxidizing agent or, presumbly, something else in between. This is a back-reaction, then, of the primarily produced or secondarily formed reducing agent with (*a*) a primarily produced oxidizing agent before the latter yields oxygen, or (*b*) with oxygen itself.

Now since we know that adenosine triphosphate can be made by the absorption of oxygen, oxidizing reduced pyridine nucleotide, we could suppose that, if the rate of reduction of carbon were sufficiently slow so that there would be time for some of this intermediate reductant which

is formed to be reoxidized by oxygen to make adenosine triphosphate, or if some of the stored sugar might be reoxidized by oxygen to make adenosine triphosphate, we should then have a quantum requirement which would be much lower than if all of the adenosine triphosphate had to be made directly by means of the immediately absorbed light. Now the reducing agent and the adenosine triphosphate are both used together; that is, one needs four equivalents of hydrogen and three molecules of adenosine triphosphate to reduce one molecule of carbon dioxide. The rate of reduction of carbon at the higher rates of photosynthesis may be ten or twenty times (sometimes more) the maximum rate of oxygen absorption and respiration. Now if carbon dioxide is taken in and reduced at a very high rate, clearly the adenosine triphosphate

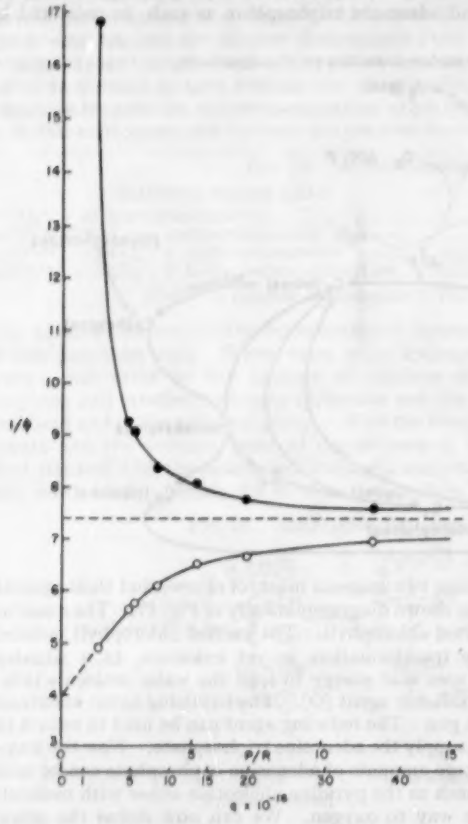
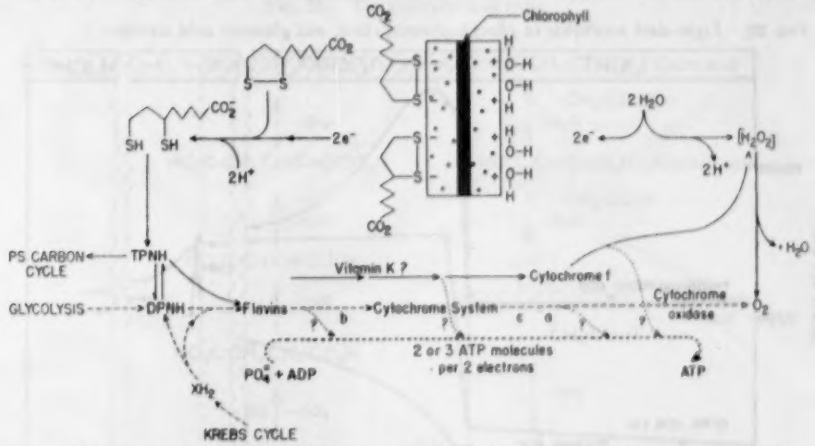


FIG. 18. *Quantum requirement of photosynthesis by* Chlorella.[6]
● Uncorrected
○ Corrected.

that would be required to reduce carbon at that rate could not possibly all be made by a respiratory mechanism, that is, by a mechanism which involves the reabsorption of oxygen and the creation of the high-energy phosphate by an ordinary combustion process. It is partly for this reason that Fig. 17 shows the broken line from the intermediate oxidant so that at very high rates of reduction the adenosine triphosphate would be made nearer to the primary photochemical reaction than at low rates of reduction. At very low rates of carbon reduction the adenosine triphosphate required to reduce it could be made by the oxidation of sugar at some other place and then brought to where it is needed for the reduction of glyceric acid. Now we can make the single likely assumption that a quantum of light can excite only one electron, not more, in the basic physical sense, and that it takes one quantum to excite one electron. Thus, there is a 1 : 1 relation between quanta and electrons and the excited electrons are the reducing agents—the [H] of Fig. 17. With this assumption it should be possible to find conditions under which the adenosine triphosphate is provided by a respiratory mechanism and the electrons are provided by the light. In that case, one should find conditions in which the

quantum requirement may be as low as four because only four electrons are needed to reduce the carbon dioxide. However, at very high rates of photosynthesis we need not only four electrons but also three adenosine triphosphate molecules, and we know that these cannot be produced by a respiratory mechanism; they must be produced also by the reoxidation of some of these electrons that are made by the primary photochemical reaction, as shown above. Then the quantum requirement must be higher. Now we can accept the quantitative relations indicated in the studies of oxidative phosphorylation in which it is known that the passage of a *single electron* from the reducing level of reduced pyridine nucleotide right up to molecular oxygen can generate about 1·5 adenosine triphosphate molecules; in other words, two electrons can generate about 3, or sometimes as many as 4 adenosine triphosphate molecules (it has not yet been completely established). So at very high reduction rates, since three adenosine triphosphate molecules are needed for every four hydrogen atoms used as reducing agents and since it takes two electrons to make at least three adenosine triphosphate molecules by reoxidation, the minimum quantum requirement under those conditions should be around six, that is, four electrons for reducing and two more to make the required three adenosine triphosphate

FIG. 19. *Suggested nature of the photochemical apparatus and its relation to other functions.*



– – – – Oxidative, or respiratory pathways. —— Reductive, or photosynthetic, pathways.

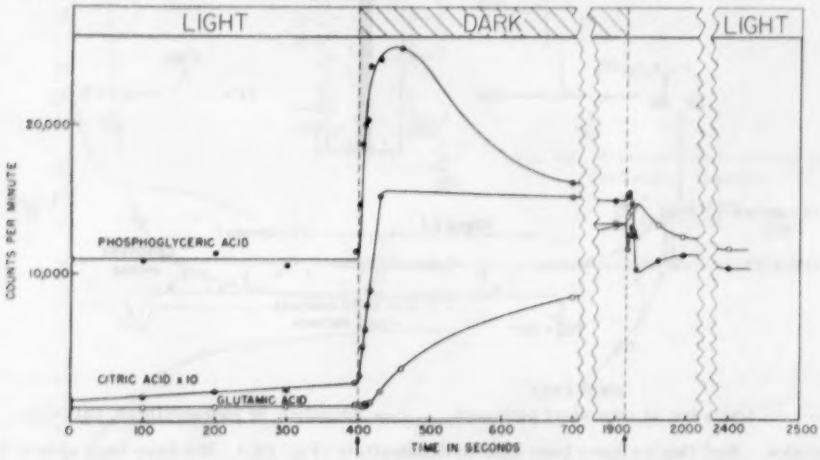
molecules. And this we have been able to demonstrate (Fig. 18).[4] We have been able to find conditions for which at high rates of photosynthesis the quantum requirement is a little more than six (6·5); and as the photosynthetic-to-respiratory rate ratio (P/R) is reduced the quantum requirement falls: we have extrapolated it to zero P/R. It is not a bad extrapolation, but it is actually from five down to four. There is no reason, I suppose, why it should not go down to 3·5. But for theoretical reasons we would prefer it to be nearer 4, although this is not essential.

Thus we have shown that at low rates of photosynthesis we can use some of the respiratory energy to make the adenosine triphosphate and thus use the quanta solely for reducing power and get a quantum requirement as low as four. At the high levels, however, we must not only make the reducing agent but we must also make the adenosine triphosphate by the recombination of the primarily formed oxidizing and reducing agents and thus produce a quantum requirement as high as six or seven. Now the question arises what do we know about the production of the reducing agent (and the oxidizing agent) and what do we know about the way in which the intermediate reductant and the intermediate oxidants can recombine to make adenosine triphosphate. And here, we enter, partly at least, the realm of conjecture; partly there is good reason for what we say.

Fig. 19 shows a proposed scheme in which this accomplished :[5] it includes the reduced pyridine nucleotide which helps run the photosynthetic carbon cycle; this is the ultimate reducing agent. In addition to the reducing agent, we must have adenosine triphosphate. This scheme provides a tentative proposal for the recombination of the reducing agent of pyridine nucleotide and the intermediate oxidant which I have here bracketed as hydrogen peroxide

although its nature is really unknown. We may combine these two through some sequence very much like the respiratory sequence, which involves flavins, cytochromes, cytochrome oxidase, and molecular oxygen, but here we by-pass to cytochrome f which is an iron–hæm compound such as exists in animal tissue, but very characteristic of green materials. We propose that through some sequence very similar to the respiratory system, which is called the oxidative phosphorylation system, we will produce adenosine triphosphate by recombining the electrons which have been raised to a reduction level such as that of reduced triphosphopyridine nucleotide by light, with the intermediate oxidant. We thus make two or three adenosine triphosphate molecules for every two electrons that pass through this system. The broken line is what happens to the respiratory system alone. The solid line is presumably what happens through some unknown sequence here to cytochrome f in the photosynthetic system. Now one may ask, where did all this come from, and this is a proper question. In the upper left-hand part of Fig. 19 we designate the reaction of the photoexcited electrons taking place at this point with the sulphur compound and in the upper right-hand part the reaction of the remaining positive charge or " hole " taking place at this point with the water molecules. Here we have already made a great jump. First of all, we have indicated some sort of structural feature for the primary photochemical apparatus. There is very ample justification for this. I might say

FIG. 20. *Light–dark transients in phosphoglyceric, citric, and glutamic acid activities.*

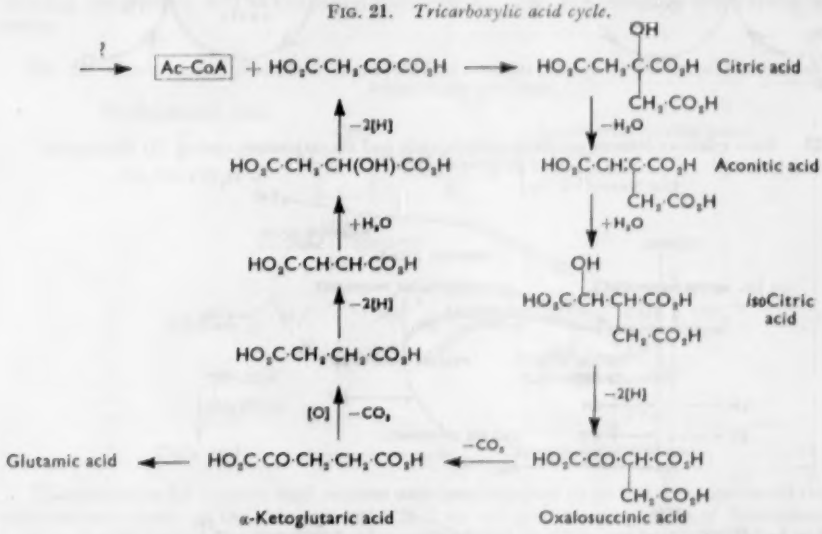


that electron-microscope pictures, particularly the most recent ones of Sjostrand [7] in Stockholm, have shown the layered structure of the small green units called the chloroplast fragments, or grana, within the individual cells. They are layered, 60 Å per layer, and the chlorophyll alternates with something else in these layers. It is suggested that this layered structure is a kind of photobattery, in which the energy is absorbed by the chlorophyll layer and lifts the electron into conduction bands where it then migrates to one side of the layer; the " hole," that is the positive charge, in an ordered lattice migrates the other way. The " holes " are immediately trapped by the donation of electrons to them, *i.e.*, by neutralization, from the water molecules. This reaction (upper right, Fig. 19) takes place at the edge of the layer, producing some intermediate oxidant which here is given as peroxide but whose identity is yet to be determined, with suitably labelled oxygen atoms. Since the " holes " are immediately trapped on one side the electrons on the other side have no place to go to and can remain for quite a long time, waiting for something to pick them up. We have proposed that the substance that picks up the electrons is a sulphur compound, a five-membered disulphide ring, which for very special reasons is capable of doing this, giving a dithiol which then can reduce the pyridine nucleotide and carry the reduction further. We prefer sulphur to the pyridine nucleotide for a number of reasons. The sulphur compound has a reduction potential slightly more reducing than reduced pyridine nucleotide (a couple of hundredths of a volt) and, therefore, it would reduce pyridine nucleotide, but the reverse would not take place readily. In addition, there was another reason for focusing our attention on this sulphur compound, which came from our studies of the

carbon cycle. This involves another one of these steady-state experiments in which we see what happens to the level of certain compounds when light is turned off. Earlier this focused our attention on ribulose diphosphate as the primary carbon dioxide acceptor. Now I am going to show you how our attention was focused on this disulphide compound as the electron acceptor in the primary photochemical reaction. Fig. 20 shows the kind of data to which I am referring.

Here, again, a steady state is established, but now instead of looking at ribulose and the sugars we are looking at something else. In addition to phosphoglyceric acid, whose activity rises, as already shown, when illumination ceases, another very interesting phenomenon occurs. While the light is on no radioactivity moves from the phosphoglyceric acid into two characteristic compounds, citric acid and glutamic acid. But immediately illumination ceases the radioactivity appears in citric and glutamic acid. The citric acid scale has been magnified ten times; there is very little citric acid, but there is an enormous change in the amount when the light is turned off. The other compound, the glutamic acid, is shown on the same scale as the phosphoglyceric acid; the changes in the two correspond (approximately quantitatively); that is, the disappearance of phosphoglyceric acid in the first few minutes in the dark is accounted for by the appearance of the radioactivity in glutamic acid. The actual amount of citric acid,

FIG. 21. *Tricarboxylic acid cycle.*



however, stops rising very quickly. This demonstrates that the carbon is passing from phosphoglyceric acid through citric acid into glutamic acid. An argument similar to that used earlier can now be made, demonstrating that this is a cyclic system and glutamic acid is the storage product. Citric acid immediately calls to mind the Krebs cycle and this has been very well established as a route for the combustion of sugars through pyruvic acid; Fig. 21 shows this cycle.

Now the only way to bring carbon from glyceric acid into this cycle is through pyruvic acid and pyruvic acid oxidase. Pyruvic acid oxidase is the system which converts pyruvic acid into carbon dioxide and acetyl coenzyme A. Without going into the details of the structure of coenzyme A, it suffices to remember that it contains thiol as an active group and it is the transfer of the acetyl group of pyruvic acid to the thiol group which constitutes the pyruvic acid oxidase reaction. Let us emphasize, once again, that the only way from phosphoglyceric acid into the Krebs cycle is througy acetyl coenzyme A *via* pyruvic acid oxidase. Fig. 22 shows this light and dark relationship diagrammatically.

Here is shown the photosynthetic cycle building up sucrose and phosphoglyceric acid and we know that in the light the carbon dioxide and water go in, with oxygen coming out, and we generate reduced carbon which goes into carbohydrates, fats, proteins, etc., in the plant. Then, gradually, these things will leak over into the respiratory system and the tricarboxylic acid cycle shown in Fig. 21. In light they pass over rather slowly from the photosynthetic cycle to the

Krebs cycle. They have to go through all the storage pools of the plant on the way. But when illumination ceases, in 30—60 seconds, a very large proportion of the material in the photosynthetic cycle, particularly the phosphoglyceric acid, passes directly into the tricarboxylic acid cycle. The possibility exists that this change may be due to a diversion by diffusion of

FIG. 22. *Schematic relations between the photosynthesis cycle, the tricarboxylic acid cycle, and storage products in the plant.*

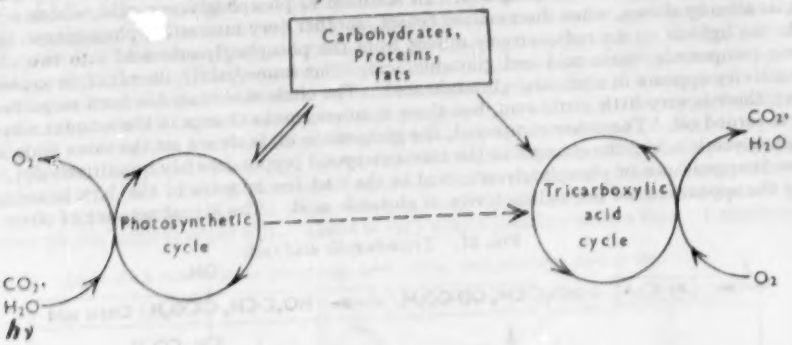
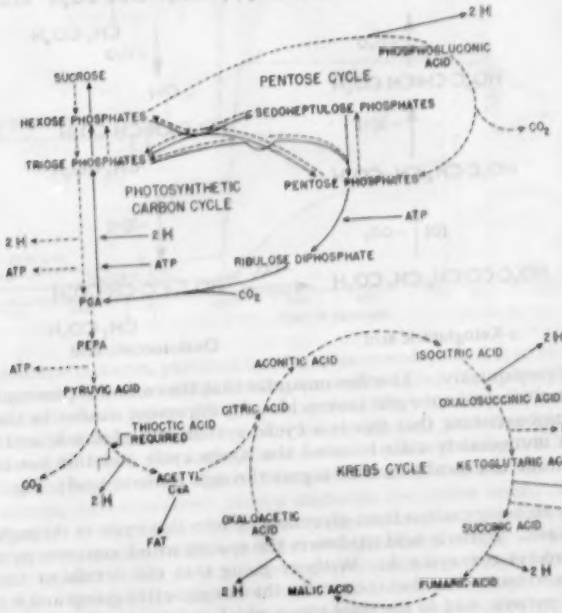


FIG. 23. *Some relations between the photosynthetic cycle and the respiratory cycles;* (1) *Krebs cycle and* (2) *pentose cycle.*



– – – – Oxidative pathways. —— Reductive, photosynthetic pathways.

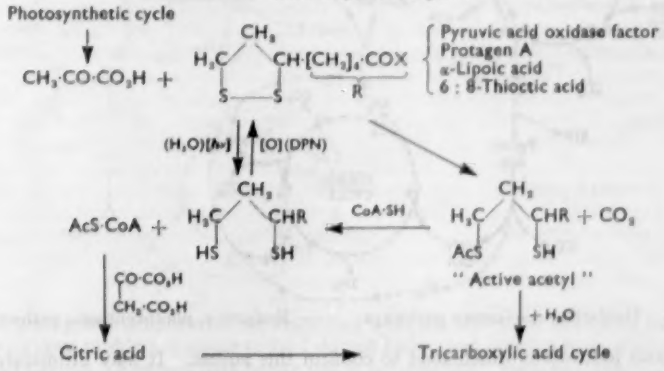
the phosphoglyceric acid of the photosynthetic pool into the normal Krebs cycle pool of the cytoplasm since it is no longer reduced in the photosynthetic cycle on cessation of illumination. We have considered this possibility but have rejected it as unlikely. The change in the rate of appearance of this carbon in (for example) citric acid upon going from light to darkness is at least 20 times the maximum change in concentration of photosynthetic (labelled) phosphoglyceric acid and hence *more* than 20 times the change in concentration difference between the

photosynthetic pool and the cytoplasmic Krebs cycle pool. A correspondingly large change in concentration gradient would be required to change the rate of diffusion from one pool to the other.*

There is then some kind of valve system between the two cycles, which in the light is closed but in the dark is opened. This is a basic notion which we must realise. Now remember that the only way for the intermediates to get into the photosynthetic cycle—the direct way—is *via* phosphoglyceric acid through phosphopyruvic acid, pyruvic acid, pyruvic acid oxidase, to acetyl-coenzyme A, and then into the cycle as illustrated above. The light in some way controls that reaction. About two years ago when the nature of pyruvic acid oxidase was discovered it turned out to be this five-membered cyclic acid—thioctic or lipoic acid—and this cyclic disulphide has some very curious properties.

The point at which the valve works is shown in Fig. 23. Here is shown the photosynthetic cycle in all the details, as well as the route from phosphoglyceric acid to phosphopyruvic acid, pyruvic acid, and right through pyruvic acid oxidase to make acetyl-coenzyme A and into the citric acid cycle. This shows in detail the two cycles that were indicated diagrammatically in Fig. 22, but it shows precisely where this valving (disulphide) compound is functioning in bringing the pyruvic acid to the acetyl-coenzyme A. Fig. 24 shows how this valving actually works.

FIG. 24. *Mechanism of photochemical control of the relations between the photosynthesis cycle and the tricarboxylic acid cycle.*



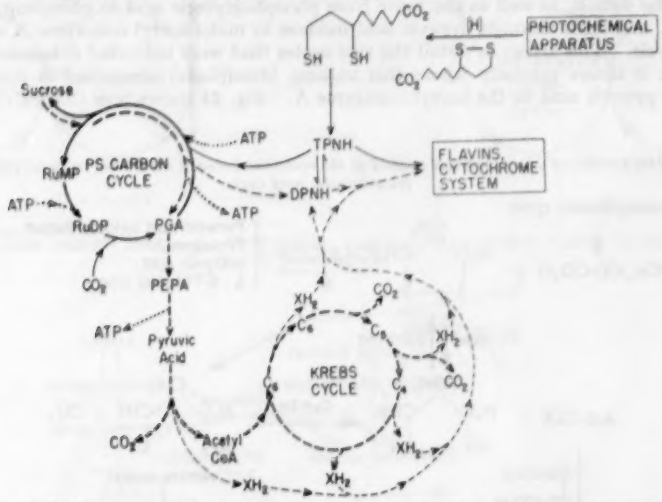
The coenzyme for pyruvic acid oxidase was demonstrated to be this five-membered ring with some carbon atoms on the side and the " X " we are now in the process of determining. It looks as though it might be a glyceride of some kind, but that has not been established and is not important for this particular argument. The important thing is to notice that in order for the two carbon atoms (α and β) of the pyruvic acid to get into the acetyl-coenzyme A we must have available the disulphide form of the thioctic (lipoic) acid. It is an oxidizing agent which oxidizes pyruvic acid to make acetyl-lipoic acid and carbon dioxide. Then the acetyl-lipoic acid exchanges with the hydrogen atom of the SH of coenzyme A (CoA) to make the dithiol and acetyl-coenzyme A which then reacts with the oxaloacetic acid to form citric acid, and thus passes into the tricarboxylic acid cycle. The dithiol, then, has to be reoxidized by something, usually pyridine nucleotide, to give the disulphide back so that it can function again. The light prevents this leakage from the photosynthesis cycle direct to the Krebs cycle. I suggest that the light does it by reducing the disulphide; at this point we do not say how the light reduces the disulphide. It shifts the equilibrium from the disulphide to the dithiol and if the compound is in the dithiol form it cannot carry out the oxidase function. Thus, we shut off the connection between pyruvic acid and the tricarboxylic acid cycle.

The final suggestion is that the light does this directly—that there is nothing between the electron which is activated by the light in the chlorophyll layers and the disulphide—that it is this which picks up the electrons off the layer of chlorophyll. The proof of this is not going to be easy. This is in a class with most of these colloidal phenomena in biological systems, in

* A question by Prof. G. E. Briggs (Cambridge) has reminded us of the apparent lack of a definitive discussion of this point.

which there is a very complex structural element involved, and the efficiency of the process depends on the existence of that complex structural element. We have been able to demonstrate, for example, that the addition of external lipoic acid to a suitable system will, indeed, increase the efficiency with which oxygen is evolved.[5] We have also shown that the addition of lipoic acid will decrease the lifetime of the excited states that are waiting for a converter. Rembember that I pointed out that the " hole " is trapped so that the electron remains and we have been able to show by flashing-light experiments that when lipoic acid is added the length of time that those electrons remain is decreased. But the direct demonstration of the suggestion that lipoic acid, or a very similar sulphur compound, is the direct receiver of the photoexcited electrons is going to be extremely difficult. However, as just mentioned,

FIG. 25. *Suggested nature of the photochemical apparatus and its relation to other functions.*



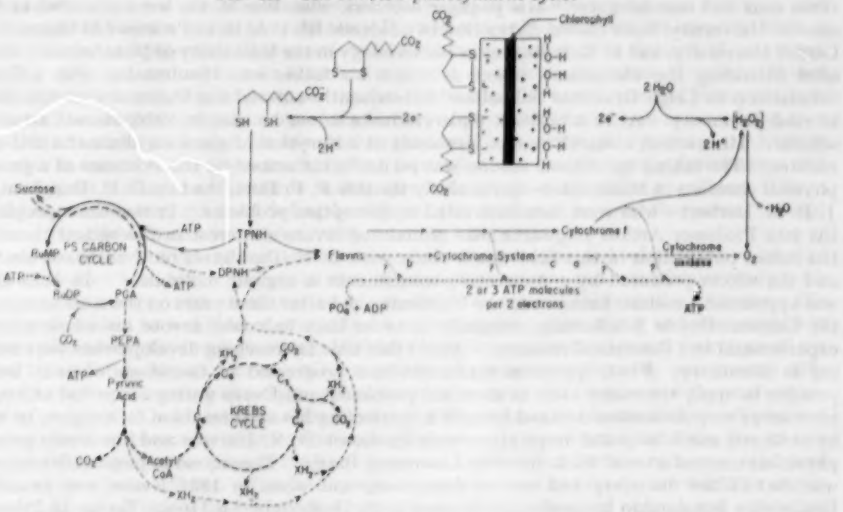
– – – – Oxidative, respiratory pathways. —— Reductive, photosynthetic pathways.

there are various indications which tend to confirm this notion. It may ultimately turn out that it is not lipoic acid itself but some derivative of it; or it may turn out that there is one compound lying between the photoexcited electrons and the sulphur, but it cannot be very much that lies between them because the valving is so swift and so complete. This constitutes one of the major problems that remain. The other is the nature of the intermediate oxidant that was mentioned earlier.

Fig. 25 is the system I have been describing, here shown in some detail, with different aspects emphasized. Here the photochemical apparatus is only indicated, producing reduced disulphide which then reduces the pyridine nucleotide which then runs the photosynthetic cycle. Some of this reduced pyridine goes back through the flavin–cytochrome system to produce the adenosine triphosphate which is necessary to run the photosynthetic cycle. The rest of it is used for the reduction. The relation between the photosynthetic cycle and the tricarboxylic acid, or Krebs, cycle is more clearly emphasized. Here is also shown the way in which adenosine triphosphate can be made in the dark, or at very low light intensities, by using up some of the stored sugar in the Krebs cycle. Coming in at the upper left-hand part of the scheme, the sugar can produce pyruvic acid which can then run through the Krebs cycle to produce reduced diphosphonucleotide, which can then run through the cytochrome system to oxygen to produce adenosine triphosphate. This would permit a quantum requirement of four. Some adenosine triphosphate may come this way, so that most of the reducing power can be used for carbon reduction and then we get a quantum yield of four. When the adenosine triphosphate requirement is so great that we have to burn some of the reduced pyridine as well, then we get a quantum requirement of six. Finally, Fig. 26 shows the whole system together—the photochemical apparatus, the photosynthetic carbon cycle, and the Krebs cycle. Also shown is the oxidative cycle which produces the adenosine triphosphate and about which least is

known. The photosynthetic cycle is well established. The nature of the primary electron is certainly not well established. The nature of the intermediate oxidant is a major problem. This last problem is one of those which we are now actively engaged with, by the use of suitable tracers. We cannot use ^{18}O because one must then know what to look for. The intermediate should be isolated and put into the mass spectrograph, and if, this intermediate is unknown, it is a little hard to get it out. So we are trying to devise other ways of tracing this intermediate. The way in which we are focusing our attention now is ^{17}O and we will use nuclear reasonance as the means of tracing. It is not going to be easy because the sensitivity is not great, but I think we will be able to identify the nature of these intermediate oxidants all included in the $[H_2O_2]$ of Fig. 26.

FIG. 26. *The complete photosynthetic cycle.*



That pretty well defines what we know and what remains to be known, at least today. How big this oxygen problem is going to be I do not know, but judging from what happened to the " Path of Carbon " I expect that before this is finished the " Path of Oxygen " is going to be as big and as complicated.

[1] Bassham, Benson, Kay, Harris, Wilson, and Calvin, *J. Amer. Chem. Soc.*, 1954, **76**, 1760.
[2] Bassham and Calvin, " Photosynthesis." Chapter in " Currents in Biochemistry," edited by D. E. Green, Interscience Publishers, Inc., New York, New York, in the press.
[3] Calvin and Bassham, " The Photosynthetic Cycle." U.N. Conference on Peaceful Uses of Atomic Energy, Geneva, Switzerland, August, 1955, Section 15C.2.
[4] Bassham, Shibata, and Calvin, *Biochim. Biophys. Acta*, 1955, **17**, 332.
[5] Bradley and Calvin, *Proc. Nat. Acad. Sci.*, 1955, **14**, 563.
[6] Racker, *Nature*, 1955, **175**, 249.
[7] Steinmann and Sjostrand, *Exp. Cell Res.*, 1955, **8**, 15.
[8] Calvin, Quayle, Fuller, Mayaudon, Benson, and Bassham, *Fed. Proc.*, 1955, **14**, 188.
[9] Mayaudon, Univ. California, Radiation Lab., 1955, 3016.

OBITUARY NOTICES.

MEREDITH GWYNNE EVANS.

1904—1952.

By the death of Meredith Gwynne Evans on December 25th, 1952, at the early age of 48 physical chemistry has lost an outstanding figure and science one of its most vital personalities.

Evans was born at Atherton, a suburb of Manchester, and was the eldest son in a family of three sons and one daughter. His younger brothers, who, like M. G., were educated at Manchester University, have shown distinction in academic life: A. G. is Professor of Chemistry at Cardiff University, and D. G. is Reader in Bacteriology in the University of Manchester. Evans, after attending the elementary school at which his father was Headmaster, won a County Scholarship to Leigh Grammar School and subsequently entered the University of Manchester to read Chemistry. After a brilliant undergraduate career he was, in 1926, elected a research scholar. His earliest research was on problems of adsorption of gases on chabazite and other zeolites. The taking up of these studies was no doubt influenced by the existence of a group of physical chemists in Manchester—particularly the late F. P. Burt, the late D. H. Bangham, and J. B. M. Herbert—who were then interested in adsorption problems. It was these people and the late Professor Arthur Lapworth who stimulated Evans's interest in theoretical chemistry. His initial publication in this field was a study with G. N. Burkhardt on "unshared electrons and the effects produced by *o*–*p*-directive substituents in organic molecules." In 1929 Evans was appointed Assistant Lecturer in the University and after three years on the staff he accepted the Clement Royde Scholarship, primarily in order that he could devote his whole effort to experimental and theoretical research. About this time far-reaching developments were occurring in chemistry. First, quantum mechanics had progressed to the stage when it became possible to apply these new ideas to chemical problems, and Evans during his period of freedom from other responsibilities devoted himself to perfecting his mathematical techniques, in which he obtained much help and inspiration from Professor D. R. Hartree and the lively group of physicists centred around W. L. (now Sir Lawrence) Bragg. The second important development was that of the discovery and use of deuterium, and when in 1934 Evans was awarded a Rockefeller Scholarship he proceeded to work with H. S. (now Sir Hugh) Taylor at Princeton where he made several experimental studies on the elucidation of the causes of the difference in behaviour of the two hydrogen isotopes. This was a happy period for Evans because Princeton at that time was a centre of discussion of the newer theoretical ideas in chemistry, and he was able to play an active part in the brilliant group, including H. Eyring, which Taylor had gathered around him.

When Evans returned to Manchester two years later, Michael Polanyi, who had already established a world-wide reputation for his work on the theory and study of atom reactions and in the application of quantum theory to chemical reactions, had been appointed to be the first holder of the Chair of Physical Chemistry. Then began that happy association which in the next few years led to the joint publication of a series of papers on the theory of chemical reactivity which have had a profound influence on all subsequent developments in this field. Among these papers was the formulation of a theory of chemical reaction now well known as "the transition-state theory." Parallel developments had been made by Eyring and his collaborators and the researches of the Manchester–Princeton school opened up a new era in the study of rate processes. Evans and Polanyi applied their ideas to the reaction of sodium atoms with a set of alkyl halides, diene-association reactions, chemiluminescence, and other processes. These studies included wide consideration of the nature of the forces of interaction between atoms and molecules and were extended by Evans and his co-workers to the structure and nature of the forces in liquids and solutions, a field to which in later years he was to devote considerable attention.

In 1939 Evans was appointed to the Chair of Physical Chemistry at Leeds. Before he had time to establish his researches there, war had started and he was called upon to undertake other duties as a member of the extra-mural group which Professor R. W. Whytlaw-Gray had previously established there in connection with the work of the Chemical Defence Experimental Establishment of the Ministry of Supply. During the period 1939—1945 he and his colleagues contributed greatly to various problems concerning the break-up of liquids ejected from munitions and the rates and theory of evaporation of small droplets of liquid of low vapour pressure.

On the cessation of hostilities Evans started a series of experimental studies of far-reaching practical and theoretical importance. He and his colleagues in Leeds elucidated the mechanism of the ferrous ion–hydrogen peroxide reaction (Fenton's reagent) and the nature of the initiation of vinyl polymerisation by this reagent. The proof of the formation of the hydroxyl radical in aqueous solution, which was produced by the electron-transfer reaction $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {\cdot}OH + OH^-$, opened up the fields of study of the nature of redox initiation of polymerisation and electron-transfer reactions in solution. He established the method of the use of the polymerisation reaction as a quantitative detector of free radicals and showed that a number of ion pairs such as $Fe^{3+}\,OH^-$, $Fe^{3+}\,N_3^-$ with light of the appropriate wavelength produced free radicals by an internal electron-transfer process and that these ion pairs were effective photosensitisers of polymerisation.

It was not unexpected when the Manchester Chair of Physical Chemistry became vacant in 1948 that Evans would return to his Alma Mater. Here he not only continued his investigations of electron-transfer and polymerisation reactions but widened his interests in theoretical chemistry. He rapidly collected around him in Manchester a host of enthusiastic researchers who looked upon M. G. as their inspirer, adviser, and leader. It was whilst at the peak of his career, and when he had become recognised as one of the leaders of physical chemistry in this country, that in June 1952 he underwent what his friends thought would be a successful operation. Although he was able to return to his Department during September, his health rapidly deteriorated and it was with quiet courage and fortitude that he faced the effects of his advancing illness. Even when his reserves of strength were fading he enjoyed the discussion of some theoretical concept with his visiting friends and was as ever very warm in his greeting.

Evans was a man of charm and kindness who won the affection and admiration of all who came into contact with him. He was a man of prodigious energy and was always ready with encouragement, advice, and assistance to his students or anyone interested in science. His interests were wide; he was fond of music, had a critical appreciation of art, and was outspoken in defence of modernistic developments. He had a keen interest in the art and technique of the film and I have often known him, when some problem he was wrestling with was causing difficulty, to leave the laboratory quietly to spend an hour or so at the cinema and then return refreshed to his work. On his return to Manchester in 1948, he bought a house with a well-planned garden and he soon became a most enthusiastic gardener. It was a great thrill for him to win a prize for a display of sweet peas at the local show and I well remember a very happy day spent with him at the Chelsea Show. This hobby was a great comfort to him during the later stages of illness. Above all things his real interest was his scientific studies and no man was ever more enthusiastic about his work. He was a fluent lecturer with a remarkable ability to stimulate young students. To Leeds and Manchester he attracted postgraduate students from many British universities and from abroad. These students and his staff colleagues will always remember his love for a discussion around the blackboard and his power of grasping the essentials of a problem presented to him and of re-stating it in an exact and elegant form. Although not a practical man he was interested in developing new experimental methods, but his main concern was with the results and their theoretical significance and the fundamental generalisations which followed. He was a familiar figure at scientific gatherings and was at his best in presenting a new theory or abstract theoretical development in a clear and illuminating manner. Scientific societies and Government committees made great calls upon him. He served as a member of the Council of the Royal Society and of the Faraday Society. He was a member of the Scientific Advisory Council of the Ministry of Supply and of many of its committees and was also a member of the Advisory Council on Scientific Policy. He was elected Fellow of the Royal Society in 1947 and was Tilden Lecturer of the Chemical Society in 1951. He was also well known abroad: he was a guest lecturer in Holland (1948), and Reilly Lecturer in the University of Notre Dame, Indiana (1951), and also lectured at scientific gatherings in Italy and France. He was happily married and is survived by his wife, one son, and one daughter.

C. E. H. Bawn.

JAMES WILLIAM McBAIN.

1882—1953.

THE story of James William McBain spreads across the pages of physicochemical science from the beginning of the 20th century to his death in Stanford, California, on March 12th, 1953. The story is international, covering extensive experiences on four continents. It began with his birth on March 22nd, 1882, the elder son in a family of five, three sisters and one brother, Clifford, in Chatham in the maritime province of New Brunswick in Canada. He was the son of a Presbyterian minister, James Affleck Frazer McBain, who was married to Mary Morrison Quin; he was a great-grandson of a former Principal of St. Andrews University, James Hunter. He seems to have had a satisfying Canadian boyhood, leading his two younger sisters and brother into one adventure after another on Silver Lake and at Port Dover. A part of his school years was passed in Rhode Island, U.S.A.

That this early education made him sound in body and mind is shown by his lifelong interest and excellence in sports and by his entry into the University of Toronto at the age of 17. At 20 years he had attained a first-class honours B.A. degree, and the M.A. degree followed in 1904. Chemistry and mineralogy were his principal concern. His orientation to physical chemistry was determined by his professors, W. Lash Miller and F. B. Kenrick, who had brought to Toronto at the close of the 19th century the new physicochemical tradition from Berlin, Göttingen, Munich, and Leipzig. It was therefore natural that McBain himself should journey, late in 1904, to the University of Leipzig where Wilhelm Ostwald was fashioning the new science with a corps of distinguished assistants including Luther, Freundlich, and Drucker. He proceeded thence, in 1905, to Heidelberg where in three semesters he achieved the Ph.D. degree in physical chemistry with G. Bredig as his professor.

From student years he passed to his first academic appointment in 1906 as lecturer in physical chemistry at the University of Bristol. It is typical of the state of physical chemical science of those years in England that, in spite of the high quality of his research achievements, it was not until 1919 that he attained a Chair, becoming the first Leverhulme Professor of Physical Chemistry in Bristol University. Already at that time he had established his leadership in the physical chemistry of soaps, detergents, and colloidal electrolytes, and had foreshadowed his important contributions to the phenomenon of " sorption " by charcoal. His scientific interests were joined with an active participation in student activities, in alumni and in adult education, in physical training and sports for the students, and in their training for future war service in the Officers Training Corps. Already he had revealed the breadth of his international interests. As a student in Europe he toured Germany and Italy in pursuit of knowledge in music and the arts. Early in 1914 he was back in Leipzig bringing to the Bunsen Gesellschaft news of Soddy's recently announced determinations of the atomic weight of thorium-lead, hearing of comparable researches by Hönigschmidt and Fajans on radio-lead. The concept of radioisotopes was established in the early days of that fateful year. We toasted the new era together in excellent Rhine wine. Twelve years later we met again at a symphony concert in Boston, Mass. McBain had decided to accept a call to Stanford University where he remained from 1927 until his retirement as Emeritus Professor in 1947. For two years longer he engaged in researches for the U.S. Office of Naval Research and then, on the invitation of Prime Minister Nehru, he accepted the position of Director, to complete and staff the Indian National Chemical Laboratory, at Poona, India. He came back to the U.S.A. on leave in 1951, and returned finally to Stanford a few months before his death in 1953.

Australasia was included in these round-the-world excursions of the Indian period. His knowledge of Russia stemmed from three visits: as a representative of the Royal Society and the American Chemical Society at the Mendelejeff Celebrations in Moscow and Leningrad in 1934; as lecturer at the Physical Chemistry Institute in Moscow in 1937; and in 1945 as one of fifteen representatives of the U.S.A. at the post-war celebration of the 220th Anniversary of the Russian Academy of Sciences. These several occasions permitted tours through Russia, the Ukraine, and Georgia, and an air-flight across Siberia.

McBain's first marriage to Anna Roeder of Karlsruhe did not survive the Anglo-German tensions of World War I. Their daughter, Janet Quin McBain, came with her father to the University of California as a visiting professor in 1926. His second marriage, on New Year's day 1929, to Mary Evelyn Laing, a scientific collaborator, member of the Science Faculty at Bristol, and Research Associate in Chemistry in the earliest years at Stanford, was a model of scientific

and social harmony. Together they fashioned a beautiful home and an incredibly lovely garden in the arid hills above Palo Alto. They had one son, John Keith McBain, the surnames recalling Miss Laing's Scottish ancestry and an uncle, John Laing, who fared forth from Scotland to South Africa in the late 19th century.

McBain's honours and services to mankind were many. Elected to the Royal Society in 1923 he became the Davy Medallist for 1939. His honorary degrees included doctorates from Brown and Bristol Universities. He was Vice-President of the Faraday Society and active in the organization of "Tables Annuelles" of physicochemical data. He was cited by the British Government for services in the Ministry of Munitions in World War I and received the Order of Merit for services to the Naval Research Board of U.S.A. in World War II. His war and post-war duties in U.S.A. were for the Office of Scientific Research and Development, the National Advisory Council for Aeronautics, and the Rubber Research Board. He was an active member and officer of Rotary International at Bristol, Palo Alto, and Poona. The guest of honour at the 1926 Fourth National Colloid Symposium in U.S.A., he was host at Stanford to the 21st Symposium, the "McBain Colloid Symposium." His Fellowship of the Chemical Society dated from 1911.

His scientific contributions are embodied in upwards of four hundred papers and two text-books dealing respectively with "Sorption of Gases and Vapours by Solids" and "Colloid Science." His earliest field of research was the physical chemistry of simple soaps, their electrical conductance, extent of hydrolysis, diffusion, transport numbers, and thermodynamic properties. Out of these researches emerged the concept of the "ionic micelle" as well as of neutral micellar units. The phase relationships of soap-rich aqueous systems form another group of his studies of soaps in which he correlated the practical conclusions of the soap-boiler with the scientific demands of Gibbs's phase rule.

His formulation of micellar structure called for an external sheath of polar groups, with the interior non-polar when present in aqueous phase. In non-aqueous non-polar media an inversion of the structure would occur with polar groups oriented to the interior of the micelle. Such inverted micelles should dissolve non-polar solvents such as hydrocarbons. In this way McBain uncovered by extensive researches the phenomenon of "solubilization." This and the complementary concept of "co-solvency," increase of solubility by the use of two or more components in the solvent medium, were the objectives of much collaborative research with his students in the final phases of the Stanford period.

Another phase of McBain's work was concerned with the surface layer of capillary active soap solutions. As is well known, Gibbs established that there should be a surface excess, Γ, of a capillary active component in a solution related to the surface tension, γ, and the chemical potential μ of the solvent by the relation $\Gamma = -d\gamma/d\mu$. Langmuir's work had indicated that the surface layer was actually a monolayer, in solutions of the lower fatty acids for example. McBain applied much experimental research and considerable ingenuity in testing the properties of surface layers, devising a moving-microtome method coupled with an interferometer to determine the composition of such surface layers. His conclusions from these experiments, as well as his studies on adhesives and adhesive action, led him to agreement with Sir William Hardy that structure existed over considerable molecular layers below the monolayer.

An experimental technique comparable to that of the moving microtome and of wide subsequent utilization was his development of the McBain–Bakr spring balance. This permitted measurements of sorption, within an entirely sealed system, by the extension of a helical spring of fused silica, the extension being determined by the weight of sorbed material on a sorbent in a bucket hanging from the helical spring. With Britton he studied the sorption of nitrogen, nitrous oxide, and ethylene on charcoal at pressures of up to 60 atmospheres, indicating their conformity to the Langmuir formulation of adsorption. The balance has proved a most valuable tool applicable even to mono-layers adsorbed on single crystal faces. McBain's use of the term "sorption" dates from 1909 to cover a complex of processes which might include adsorption, diffusion, absorption, and solid solution. The particularized names such as "adsorption," etc., "should be restricted to cases in which it has been proven to consist of only one of these." Phenomena in sorption which proceeded progressively through long periods, even years, he labelled "persorption."

A further illustration of the elegance of his experimental achievements is to be found in a series of studies between 1935 and 1941 of air-driven centrifuges which he utilized for colloid problems and sedimentation equilibrium measurements. The simplicity of the centrifuges was coupled with their inexpensiveness.

Quiet, kindly, sympathetic, meticulously honest in scientific and personal relations, he

endeared himself to a large host of students and scientific colleagues. Across wide areas of the British Commonwealth he left the enduring mark of his presence and, in his adopted country, he achieved the opportunity to exercise, with full scope, the great gifts for science which were so abundantly his.

HUGH TAYLOR.

SYDNEY GLENN PRESTON PLANT.

1896—1955.

SYDNEY GLENN PRESTON PLANT, the only son of Alfred Glenn Plant, was born at Leicester on November 5th, 1896, and he died in Oxford on September 10th, 1955, after a short illness and an operation. He was educated at Wyggeston Grammar School, Leicester, while Canon James Went was Headmaster, and he received his early scientific training under E. J. H. Eames who was Science-master at Wyggeston in his day. He won an Open Scholarship in Natural Science to St. John's College, Oxford, in March 1915, and, as he was not accepted for military service, he went up to Oxford in the following October. He obtained a First Class in the Final Honour School of Chemistry and took his B.A. degree on July 6th, 1918. At St. John's he was a pupil of M. P. Applebey.

Plant was appointed Demonstrator in Organic Chemistry in the University of Oxford in July 1919 and elected to a Senior Demyship at Magdalen College in December of the same year. He became a University Lecturer in Organic Chemistry in 1924 and, at the time of his death, he was senior Lecturer and Demonstrator in the Dyson Perrins Laboratory. In 1920 he gave his first lectures in the Chemistry School at Oxford, and from that time until he died, he lectured regularly, never missing a year. At the beginning of his career he gave the fundamental lectures on general organic chemistry, and he will no doubt be best remembered, by many generations of undergraduates, for his lectures on Stereochemistry and on Sugars and Polysaccharides. He was a most gifted lecturer with great ability to select and condense the essentials of complex and difficult subjects, and few who heard him will forget the impact of his lectures which were quite outstanding, even in Oxford where good lecturers are not rare. As a demonstrator, too, he was unfailingly helpful and stimulating, especially to the undergraduate struggling with his first attempts at practical organic chemistry.

Plant's earliest researches were on the absorption of ethylene and propene by sulphuric acid and were of a semiphysical nature, carried out under N. V. Sidgwick. This work earned him the degree of B.Sc. in 1920. Then he turned to pure organic chemistry and worked under W. H. Perkin, junior, for the degree of D.Phil., which he received in 1923. It was at this time that he began his work on tetrahydrocarbazole * (I), his interest in this substance having arisen from its possible relation to strychnine and its structural similarity to tetrahydroharmine.

He began by investigating its nitration and found that, whereas tetrahydrocarbazole itself is nitrated in sulphuric acid to the 6-nitro-compound, its 9-acyl derivatives are nitrated in acetic acid to give 9-acyltetrahydro-7-nitrocarbazoles, together with substances that have been formed by addition to the 10 : 11-double bond.[1,2,3] 9-Benzoyltetrahydrocarbazole thus afforded 9-benzoyl-1 : 2 : 3 : 4 : 10 : 11-hexahydro-10-hydroxy-11-nitrocarbazole which was converted, by alkali, into δ-*o*-benzamidobenzoylvaleric acid. 9-Acetyltetrahydrocarbazole, on the other hand, afforded the 9-acetylhexahydro-10 : 11-dihydroxycarbazole (II). This substance was also obtained later [4] by bromination of 9-acetyltetrahydrocarbazole. The compound (II) was found to undergo interesting rearrangements with acetic anhydride and with alkali and afforded two isomeric compounds, $C_{12}H_{13}ON$ (III and IV), both of which were different from two further isomerides, $C_{12}H_{13}ON$ (V and VI), obtained by bromination of tetrahydrocarbazole itself and its 9-benzoyl derivative respectively.[4,5] The compounds tetrahydro-11-hydroxycarbazolenine (V) and tetrahydro-1-hydroxycarbazole (VI) were both found to dimerise with loss of water, in

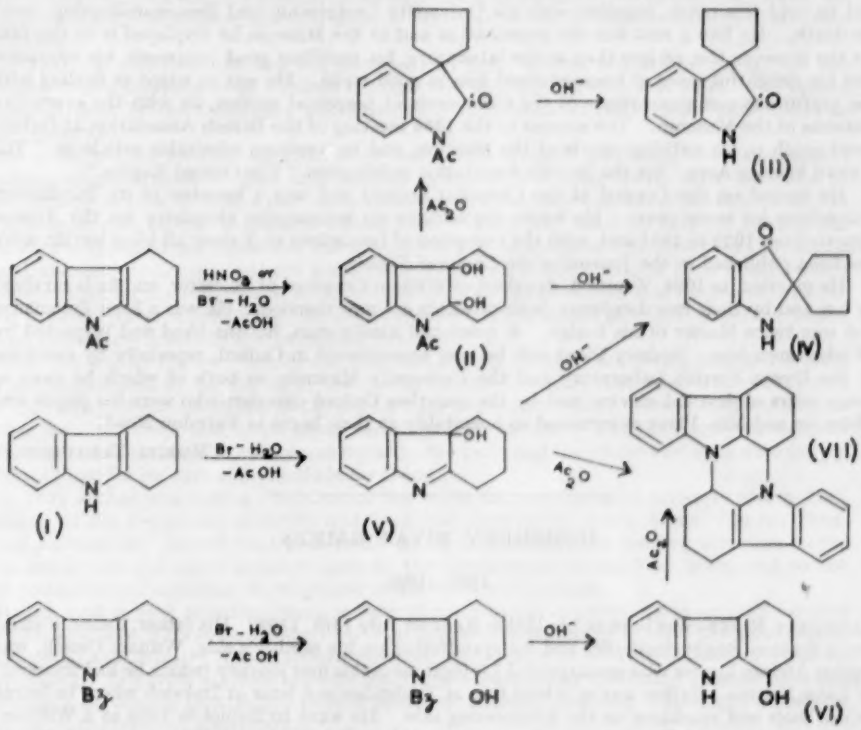
* In this Notice tetrahydrocarbazole refers to 1 : 2 : 3 : 4-tetrahydrocarbazole and hexahydrocarbazole to 1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole.

[1] Perkin and Plant, *J.*, 1921, **119**, 1825.
[2] *Idem*, *J.*, 1923, **123**, 676.
[3] Plant, *J.*, 1936, 899.
[4] Plant and Tomlinson, *J.*, 1931, 3325.
[5] *Idem*, *J.*, 1933, 298.

the presence of acetic anhydride, thus affording 1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-octahydro-1 : 9-9′ : 1′-dicarbazolylene (VII). The constitutions of these substances were finally elucidated in collaboration with Sir Robert Robinson,[6,7,8] and these complex reactions can most easily be summarized in the annexed chart.

It is interesting that Plant's discovery [9] in 1925 of the toluene-soluble covalent sodium and potassium compounds of *cyclo*pentane*spiro*oxindole (III) [at that time considered to be the indoxyl (IV)] was of great interest to Sidgwick because these substances were the first co-ordination compounds of sodium and potassium to be recognised.

Plant's life-long interest in indoles and carbazoles grew out of his early work on tetrahydrocarbazole : with his pupils he has published some eighty papers on researches mainly in this field. Nitration, bromination, and the Friedel–Crafts substitution of many simple and complex indoles and carbazoles were investigated, and the constitutions of the products of these reactions



elucidated. In many instances it was necessary to develop unambiguous methods to settle the structures of compounds which were formed by application of the Fischer reaction to *meta*-substituted phenylhydrazones. Plant and his pupils have established that in general only the simpler indoles (tetrahydrocarbazole, dihydropentindole, dimethylindole, etc.) form addition products and that *N*-acylated indoles normally undergo substitution *meta* to the >N·COR group, *i.e.*, the orientation is not controlled by the nitrogen atom of the indole nucleus. The main point of attack is generally at a *meta*-position furthest from the ring-junction when two *meta*-positions are present.

The reductions of many heterocyclic compounds were investigated by Plant and his collaborators and they have isolated *cis*- and *trans*-hydro-derivatives in a number of cases. During

[6] Plant and Robinson, *Nature*, 1950, **165**, 36.
[7] Plant, Robinson, and Tomlinson, *ibid.*, p. 928.
[8] Plant and Tomlinson, *J.*, 1950, 2127.
[9] Plant and Sidgwick, *J.*, 1925, **127**, 209.

the war Plant worked with a team at the Dyson Perrins Laboratory investigating vesicant substances, and the results of these researches were published in a series of papers in the *Journal* in 1948. Since then he had become interested in the preparation and investigation of the five possible isomeric indolocarbazoles and a series of papers on these and related topics has appeared in the past six or seven years.

Plant probably rose to his greatest heights as a supervisor and director of research. His own work provided a steady flow of research problems not too difficult for the beginner, yet admirable for the training of the young worker: he selected topics for his pupils with unfailing good judgment and invariably guided their work to successful conclusions. Those who came under his influence are the better chemists for the excellent training they received under his keen and kindly supervision: they owed him a great debt and they have repaid it by the good use they have made of his inspiration.

In 1928 Plant was appointed Secretary to the Delegates of the University Museum at Oxford and he held this office, together with his University Lectureship and Demonstratorship, until his death. He had a real flair for organisation and at the Museum he displayed it to the full. At the Museum too, no less than at the laboratory, his unfailing good judgment, his tolerance, and his delightful sense of humour stood him in good stead. He was as adept at dealing with the gratuitous communications of the discoverers of perpetual motion, as with the every-day business of the Museum. The success of the 1954 meeting of the British Association at Oxford owed much to his untiring efforts at the Museum, and he wrote an admirable article on "The Oxford Science Area" for the British Association publication "The Oxford Region."

He served on the Council of the Chemical Society and was a member of its Publication Committee for some years. He wrote the sections on heterocyclic chemistry for the *Annual Reports* from 1928 to 1931 and, with the exception of two letters to *Nature*, all his scientific work has been published in the *Journal of the Chemical Society*.

He married, in 1924, Winifred, daughter of William Crawford of Leicester, and he is survived by her and by their two daughters, both of whom are now married. He was a keen Freemason and was twice Master of his Lodge. A quiet and kindly man, he was liked and respected by all who knew him. Sydney Plant will be long remembered in Oxford, especially by everyone at the Dyson Perrins Laboratory and the University Museum, to both of which he gave so many years of devoted service, and by the countless Oxford chemists who were his pupils and whom he and Mrs. Plant entertained so hospitably at their home in Farndon Road.

MURIEL TOMLINSON.

HUMPHREY RIVAZ RAIKES.

1891—1955.

HUMPHREY RAIKES was born at Ide Hill in Kent on July 14th, 1891. His father, Canon Raikes, was a famous Rugby footballer and his grandfather on his mother's side, William Oswell, was a great African hunter who accompanied Livingstone on his first journey (which he had financed) to Lake Ngami. Raikes was at school first at Tonbridge and later at Dulwich where he learnt to use tools and machines on the Engineering side. He went to Balliol in 1910 as a Williams Exhibitioner to read Chemistry, and gained the Abbott Scholarship in 1911 and a first class in the Final Honour School of Chemistry in 1914. Raikes was a keen soldier (his grandfather had served as a civilian in the Crimean War) and while an undergraduate he held a Special Reserve Commission in the Buffs and he went with them to France in the autumn of 1914. He was severely wounded in the shoulder in May 1915 and after his recovery transferred to the Royal Flying Corps, in which he took a leading part in the development of the early bombing techniques and became chief experimental officer. He was a member of the Royal Air Force Mission to the United States in 1918 and for his services to flying he received the Air Force Cross in that year.

He returned to Oxford as Lecturer in Chemistry at Balliol and in 1919 was elected to a Fellowship at Exeter College where he later became Sub-Rector. The school of Physical Chemistry was just beginning to grow and Raikes's contribution as Treasurer of the Balliol and Trinity laboratories was invaluable. His unselfish and tidy housekeeping saved his colleagues from so many headaches and he always found means of providing the space and the apparatus we needed. His own interest was in electrochemistry and those of us who were

working in that field owed much to his constructive suggestions and help, so that his own contribution must not be measured by the small number of papers he published. He rejoined the R.A.F. in 1935 as Chief Instructor to the Oxford University Air Squadron with the rank of Wing Commander.

Raikes's striking personality and breadth of interests had marked him out for action in a wider sphere and in 1927 he was appointed Principal of the Witwatersrand University of Johannesburg. From his grandfather he had inherited an interest in the African continent and his grandfather's sketch map of his journeys used to hang in his study. Those who had the perspicacity to appoint him could not have made a wiser choice. The University with 1500 students had just moved to an almost empty site at Milner Park, and the Medical School at Hospital Hill was housed in the unfinished fragment of the final building. Raikes saw a great opportunity, and his constructive mind, his care for detail, his æsthetic sense of fitness, his determination, and his untiring energy, found expression in the fine group of buildings which the University and the Medical School now enjoy. When he retired in 1954 the number of students had trebled.

In 1931 the University library was destroyed by fire. Raikes was undaunted by the loss and used it as a stepping stone towards the new and finer library that was built. His appeal aroused interest in the University and brought contributions of books from universities in many countries.

He never lost his love for scientific work and he did much to encourage the development of post-graduate studies in pure and applied sciences. For some years after he came to Johannesburg he took an active part in the teaching of chemistry and one of his first tasks was the re-organization of the University laboratories. When war came in 1939 he advised the older men to finish their courses and the younger to join up at once. He served as O.C. of the Rand University Training Corps and his work as Chairman of the Aptitude Tests Board, which was responsible for the methods of personnel selection for the South African Air Force, was the major influence in establishing the National Institute for Personnel Research under the South African Council for Scientific and Industrial Research.

After the war he felt very keenly the debt that society owed to the young men and women who had contributed to the war effort and he did his best to ensure that those who could profit by a University education should not suffer for their devotion to duty. Nearly 3000 ex-soldiers entered the University, and its numbers rose from 3000 to 5000. Thanks largely to Raikes's skilful improvisation the University was equal to the task, and the ex-Service men were deeply grateful to him for his care and solicitude for them.

In 1932 Raikes was elected President of the South African Chemical Institute and in 1947 President of the Associated Scientific and Technical Societies of South Africa. In his Presidential Address on "Liquid Fuel from Coal" he showed foresight in drawing attention to the limits which coal and water supplies place on the development of the Vaal basin, and to the great possibilities of industrial development in the Eastern Transvaal.

Raikes took a very broad progressive view of the place of a university in modern life and under his guidance Witwatersrand developed on lines which enabled it to meet the varied needs of commerce and industry as well as to strengthen its position as a centre of academic studies and research. His great services to education were recognized by Honorary Degrees from the Universities of Bristol, Cambridge, Cape Town, and Toronto, and only a fortnight before his death by Witwatersrand University.

I was very proud of him as he had been my pupil, from whom I had learnt many lessons. The days I spent with him going round the Witwatersrand University were a great education. The design of the Great Hall in which he had overcome the acoustic problems, the grouping of the buildings round the quadrangle, the keen schools of research in so many departments, the collection of Africana, the lay-out and equipment of the dental hospital equal to anything in the world, are all a monument to Raikes's taste and judgment. But his influence went far beyond buildings and research. He was loved by his students for whom he did so much. In his final charge to them he spoke of "the divine gift of statesmanship." This he himself possessed. It was this quality, together with his modesty, that won the respect and confidence of those he did not hesitate to criticize if he felt it necessary. He had studied the political problems of the Union, he had learnt Afrikaans, and his wise counsels will be sorely missed in South Africa.

HAROLD HARTLEY.

RALPH WILLIAM EWART STICKINGS

1895—1955.

R. W. E. Stickings, who was born in Mitcham on March 20th, 1895, was a science graduate of London University. During the 1914—18 war he saw active service with the R.A.M.C. in France and was awarded the O.B.E.

In 1919 he came to May & Baker Ltd. at Wandsworth as a research chemist. For some years he was engaged in the preparation of heterocyclic compounds containing arsenic for the evaluation of their trypanocidal properties. In 1927—28 he was either sole or joint author of a series of three publications thereon in the *Journal*, his name figuring in relevant patent literature.

In 1924 he migrated from research to production within the May & Baker organisation, becoming Works Manager first at the Wandsworth factory and subsequently at both Wandsworth and Battersea; and a "production man" he remained until the end of his days. The year 1934 saw the transference of the firm to its present site in Dagenham. In 1940 Mr. Stickings became the first Director of Production.

The years between his appointment to the Board and his nomination in 1952 as Deputy Managing Director were for Mr. Stickings a period of increasing activity in the interests, not only of the parent company, but of its subsidiaries at home and overseas. The number of his directorships within the organisation and the extent of his travels on its behalf are indicative of his wide powers of leadership and of the high esteem in which he was held.

Business apart, he was a man of wide interests. He had a kindly disposition as befitted one who was a Deacon of the Congregational Church.

He died in Brentwood District Hospital, Brentwood, Essex, on December 3rd, 1955, leaving a widow, two sons, and a married daughter. A third son lost his life in the advance towards Arnhem.

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